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PART I

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THE UNIVERSITY OF ALBERTA

DECOMPOSITION OF DIPHENYLIODONIUM-2-NAPHTHALENETHIOLATE
IN VARIOUS SOLVENTS

by
WILLIAM J. REBEL

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ABSTRACT

Evidence exists in the literature to demonstrate that diphenyliodonium salts are ionic compounds. In theory certain diphenyliodonium compounds could possess covalent bond character, and these compounds when decomposed should do so by a free radical mechanism.

The synthesis of diphenyliodonium-2-naphthalene-thiolate and its decomposition in various solvents are discussed. Evidence is presented to show that diphenyliodonium-2-naphthalenethiolate does possess at least some covalent I-S bond character, and this compound does decompose by a free radical mechanism. The evidence is based on ultraviolet spectra and analyses of the product distributions in various solvents.

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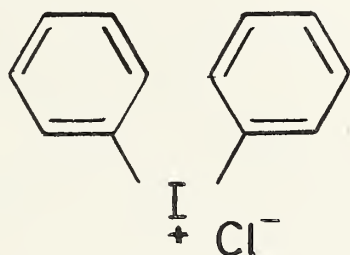
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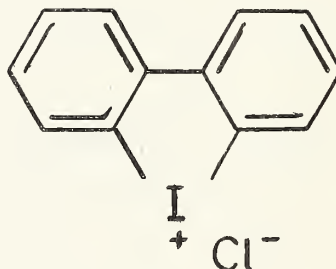
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INTRODUCTION

Iodonium salts belong to a group of organic iodides in which the halogen atom exerts a valence greater than one. They are derivatives of the hypothetical base H_2IOH and are therefore related to other "onium" compounds such as the ammonium and sulfonium compounds. Iodonium salts have the general formula R_2IX in which R is an aryl or vinyl radical. Some structures for iodonium salts are shown below:



VI diphenyliodonium
chloride



XI dibenziodolium
chloride

A study of the decomposition of iodonium salts is rewarding for several reasons. First, the thermal decomposition of iodonium salts is useful in organic syntheses. Second, the decomposition of iodonium salts is interesting from the standpoint of reaction mechanism. This thesis is mainly concerned with the latter. The reaction mechanism may involve ions or free radicals, depending upon the experimental conditions and the nature of the cation and anion.

The literature survey, therefore, is concerned with the work carried out on the decomposition of iodonium salts. Attention will be focussed on a possible ionic or free radical mechanism.

LITERATURE SURVEY

Iodonium compounds are decomposed by heat and in this respect they resemble other onium compounds (1). For example, diphenyliodonium iodide on heating decomposes to give iodobenzene:

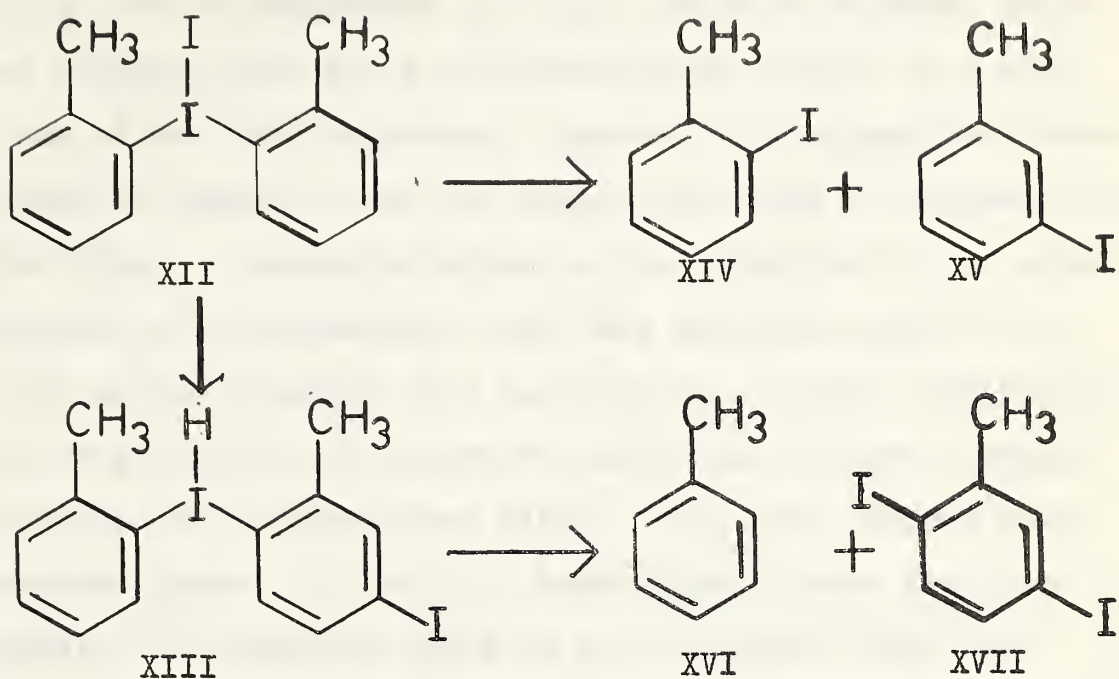


The decomposition temperature of an iodonium salt depends upon the nature of the anion as well as the cation. For the same cation Sandin found that the decomposition temperature of an iodonium salt varies with the nucleophilicity of the negative ion.

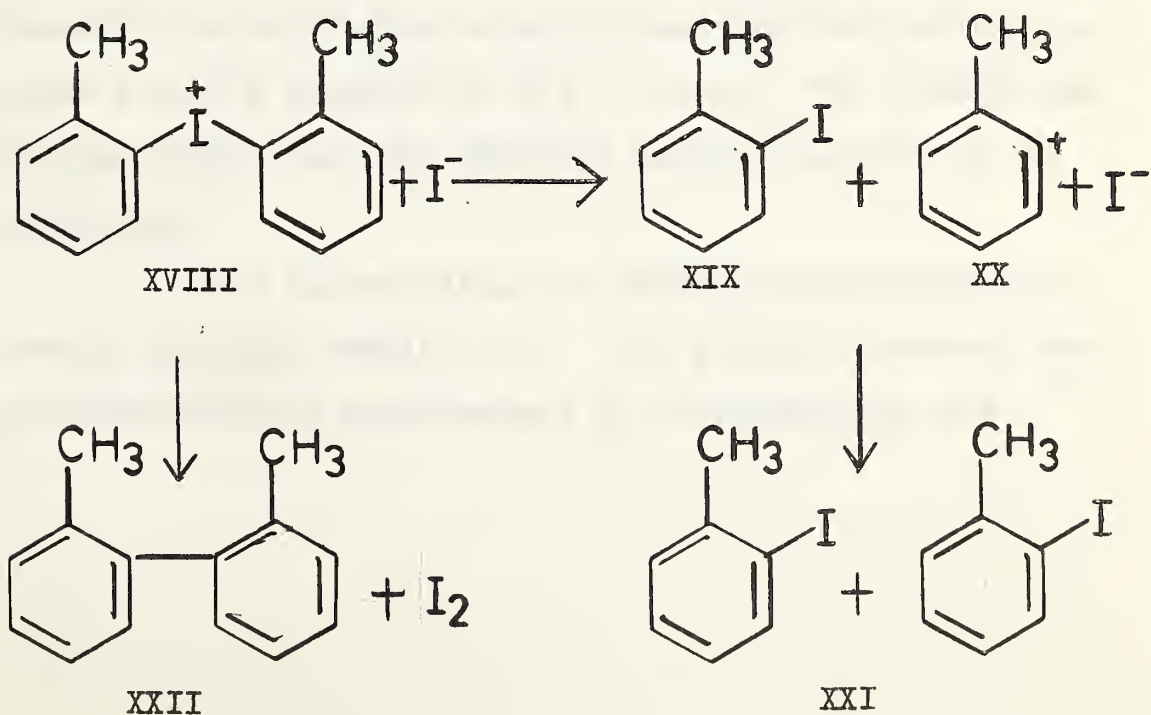
Lucas, Kennedy, and Wilmont (2) studied the decomposition of di-*o*-tolyliodonium iodide which decomposes by way of an intermediate positively charged ion. According to these workers, there are two possible mechanisms by which the decomposition might take place (a) migration of the iodide iodine to one of the benzene rings in a position ortho or para to the C-I bond, followed by the scission of the C-I bond; (b) the scission of a C-I bond, followed by the attachment of the resulting positive organic ion to the negative iodide ion. The two mechanisms are pictured on the next page.

If the two iodine atoms are held together by a covalent bond (XII), the migration of iodine to an ortho or para position on the benzene ring is quite plausible.

(a) Migration first:



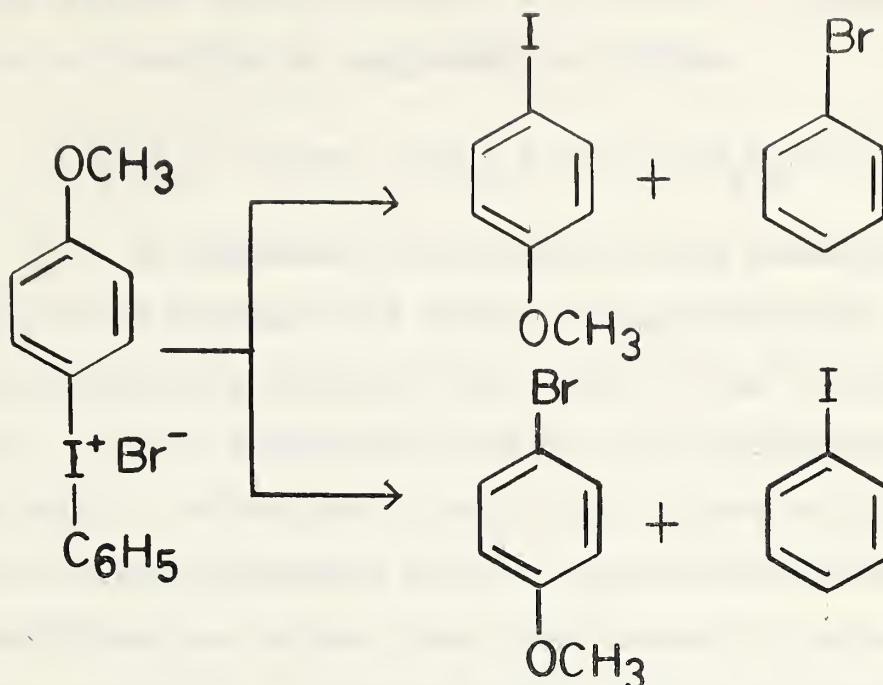
(b) Scission first:



If migration is the first step, then scission of a C-I bond in the hypothetical intermediate (XIII) should lead to the formation of a mixture of equal parts of o-iodotoluene (XIV) and m-iodotoluene (XV), or a mixture of equal parts of toluene (XVI) and 2,5-diiodotoluene (XVII), or a mixture of the four compounds. However, if the original compound is ionized, then the iodide ion would not migrate to the ring. A mechanism might be the formation (1) of equal amounts of o-iodotoluene (XIX) and positive o-tolyl ion (XX) by the breakage of a C-I bond and (2) the combination of this ion with the negative iodide ion to form a second molecule of o-iodotoluene (XXI). This would afford pure o-iodotoluene. If both C-I bonds should break simultaneously, the products would be o,o'-bitolyl (XXII) and iodine. Lucas and his co-workers found the decomposition product to be pure o-iodotoluene. This indicated that the iodonium ion split into o-iodotoluene and the positive o-tolyl ion by a scission of the C-I bond. The o-tolyl ion and the iodide ion then produced another molecule of o-iodotoluene.

The decomposition of phenyl-p-anisylodonium bromide has been examined (3). The possible products are p-iodoanisole and bromobenzene or p-bromoanisole and

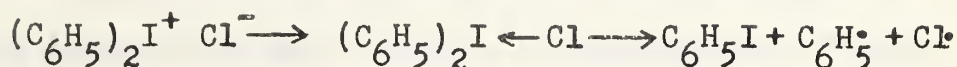
iodobenzene:



It was found that 87% or more of the decomposition followed the first reaction scheme. The decomposition occurred in such a way that the more electronegative radical (p-anisyl) remained attached to the iodine atom.

Sandin, McClure and Irwin (4) found that diphenyliodonium chloride reacts with mercury in boiling n-propyl alcohol to produce phenylmercuric chloride. In view of this result, Sandin and co-workers assume that in the decomposition of an iodonium salt part of it at least can decompose by way of a nonionic mechanism. The assumption is made that in the iodonium salt the central iodide atom is able, by expanding its valence shell to act as an acceptor for the chloride ion. Subsequent transformations of this complex result from the tendency

of the central atom to revert to an octet. A probable course of reaction is suggested as follows:



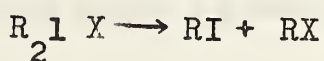
In agreement with Sandin's work Nesmeyanov, Makarova and Tolstaya (5) report diphenylchloronium and diphenylbromonium salts are less stable than iodonium salts. This is especially true for the diphenylchloronium salts. On the whole these salts behave very similarly to diphenyliodonium salts. Diphenylchloronium and diphenylbromonium iodides form phenylmercuric iodide with metallic mercury in alcoholic medium due to a homolytic cleavage. It is difficult to explain the homolytic cleavage unless the formation of a covalent form of diphenylhalonium salt is assumed.

Professor H. J. Lucas (2) has pointed out the important role exerted by the metal in the decomposition. He suggests the possibility of an intermediate, undissociated complex which decomposes at a lower temperature than the salt would otherwise. Such a reaction mechanism would not necessarily involve the formation of free radicals. On this basis also, the decomposition with and without a metal would not necessarily have to proceed via similar mechanisms.

Medlin (6), by means of X-ray investigations, has shown that the distance between the iodine atoms in

diphenyliodonium iodide is 3.55\AA^0 , which is compatible with an ionic and not a covalent structure. The stability against interchange of the iodine atom in diphenyliodonium iodide has been studied. Juliusburger, Topley and Weiss (7) crystallized this salt from ethanol and water containing sodium iodide made radioactive by neutron bombardment. The resulting solid was strongly radioactive. Diphenyliodonium hydroxide from it was converted to the iodide with inactive sodium iodide and was inactive. Therefore the interchange occurred with the negative iodine only.

Masson and Race (8) have called attention to the important fact that bis-(p-chlorophenyl)iodonium hydrogen sulfate can exist as an oil form and is partly soluble in chloroform in which it undergoes fission to some extent, producing the aromatic iodo compound. With reference to these properties, Masson and Race have made the important observation that it "points to marked polarizability of the anion by the cation," and that "it seems clear that any strong interionic polarization, the effects of which are to induce, as has been mentioned, properties tending toward those of covalent compounds, must play an important part in initiating the wholly irreversible fission which all iodonium salts undergo when they are heated,



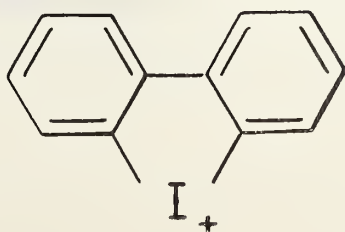
wherein the hitherto anionic X becomes covalently attached to one of the radicals R."

Beringer (9) reported that with few possible exceptions the reactions of diphenyliodonium salts with bases proceed by nucleophilic rather than radical attack on the 1-carbon of diphenyliodonium salts to give iodobenzene and the phenyl derivatives of the bases. It was observed that reactions were faster with strong base than with weak base and in general paralleled the efficiencies of the reactions with similarly charged ethylenesulfonium ions. Also, in no case were benzene and biphenyl, the expected by-products of a radical chain reaction involving phenyl radicals, found. Finally, while mercaptans are known to be efficient terminators of radical chain reactions, the phenylation of several sulhydryl groups have been reported.

To provide further tests for this mechanistic hypothesis 2- and 3-nitrodiphenyliodonium bromide were investigated. In all cases the attack of the bases occurred at the 1-carbon of the rings bearing the nitro groups, with formation of iodobenzene. The rates of reaction apparently increased in the order: unsubstituted < 3-nitro < 2-nitro diphenyliodonium bromide (as did yields, in general). Beringer states that enhanced reactivity is expected on the introduction of a nitro group, on the basis that there would be more interaction of an electron-with-

drawing group with a ring electron-rich in the transition state (during nucleophilic attack) than with a ring neutral in the ground state.

H. G. Heal (10) reviewed the publications to 1958 on iodonium salts, and he states there can belittle doubt that these substances (iodonium salts) are really ionic. While it is formally possible to write chloronium, bromonium and iodonium salts as fully covalent structures, physical evidence indicates these compounds are really ionic. First, the solubilities show ionic character, and water, liquid ammonia and lower molecular weight alcohols are the best solvents. Secondly, the solutions are good electrical conductors, and undergo instantaneous metathetical reactions with, e.g. silver nitrate. Thirdly, diphenyliodonium iodide exchanges half of its iodine instantaneously, but the other half will not exchange. Fourthly, the compounds of colorless anions are themselves colorless, which seems to rule out any pronounced degree of covalent bonding of the anion. Furthermore, the orbitals available for bonding in divalent iodine are like those in divalent oxygen and sulfur, since the two carbon-halogen bonds in the halogenonium salts are nearly at right angles. The existence of unusually stable chelate halogenonium ions such as



which could only be formed without strain if the bonds from the halogen were collinear, supports this belief.

J. D. Roberts and co-workers (11) undertook an extensive study of the hydrolysis of diaryliodonium salts. These workers reported that substantial hydrolysis does not occur by either an S_N1 or an S_N2 mechanism unless the nucleophilic character of the associated anion is negligibly small. For this reason anions possessing very little nucleophilic character, such as fluoride, fluoroborate, tosylate and trifluoroacetate were selected in the hope that hydrolysis might take place exclusively by one path.

It was hoped that a study of the products from the hydrolysis of unsymmetrical iodonium salts would indicate the operative mechanism, since it was anticipated that substituents would strongly influence the product distribution in a manner which would allow distinction to be made between reaction by an S_N1 or an S_N2 mechanism. The products to be expected for S_N2 hydrolysis of 3-nitrodiphenyliodonium ion are m-nitrophenol and iodobenzene. In contrast, S_N1 hydrolysis should give predominantly m-nitroiodobenzene and phenol. However it was found that the hydrolysis of 4-methoxydiphenyliodonium salts yielded all four possible products, p-iodoanisole, iodobenzene, phenol and p-methoxyphenol.

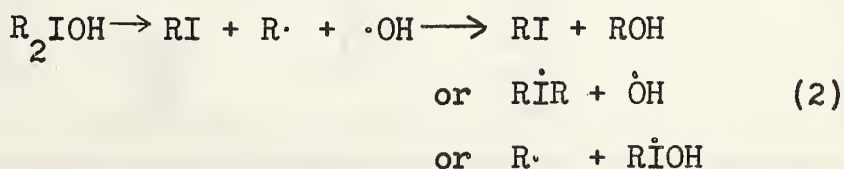
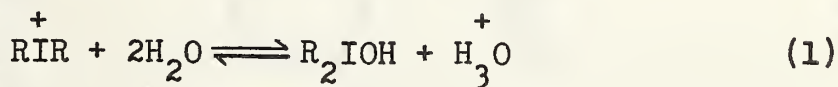
At about the same time this work had commenced, Beringer and associates (12) reported that the thermal decomposition of diphenyliodonium halides in various solvents was strongly catalyzed by trace amounts of cupric and cuprous copper. Roberts also found the hydrolysis of iodonium salts to be similarly catalyzed. Furthermore, it was found that the product distribution in the Cu^{II} and Cu^{I} catalyzed hydrolyses of 4-methoxydiphenyliodonium tosylate or trifluoroacetate in various solvents was the same as in the uncatalyzed reaction.

The hydrolysis of 3-methyldiphenyliodonium tosylate, in the presence of micromolar amounts of Cu^{II} , gave a mixture of all four possible products, iodobenzene, phenol, m-iodotoluene, and m-cresol and the same products in the same distribution resulted from the Cu^{I} catalyzed reaction. Hydrolysis is catalyzed by micromolar amounts of cupric or cuprous copper. Cupric copper is not in itself an effective catalyst, but becomes so by reduction to the cuprous state. This reduction is retarded by oxygen and acid. The iodonium salt may act as the reducing agent, but the oxidation product has not been identified. It was also shown that not only does acid inhibit the reduction of cupric copper, but the uncatalyzed reaction in water is retarded by acid as it is formed, and by acid when initially added. The two iodine-carbon bonds of 3-methyldiphenyliodonium tosylate rupture with almost equal ease.

It is apparent that the direction of C-I bond fission is remarkably insensitive to the substituents present. This is strikingly demonstrated in the hydrolysis of 3-nitro-4'-methoxydiphenyliodonium tosylate. The Cu^{II} catalyzed hydrolysis afforded an astonishingly even split between the two possible directions of C-I fission (Fig. 1).

The distribution of products from this hydrolysis is surprisingly insensitive to the nature of the phenyl substituents. A plausible reaction mechanism must necessarily account for this lack of substituent effect and the pronounced catalytic effect of cupric copper, and it seems therefore unlikely that the reaction proceeds by either an $\text{S}_{\text{N}}1$ or an $\text{S}_{\text{N}}2$ mechanism. The results suggest that some sort of homolytic mechanism is involved.

Roberts suggests a possible mechanism for the uncatalyzed hydrolysis which satisfactorily accounts for retardation by acid and the lack of substituent effects as follows:



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description of the situation in the country at the end of 1954.

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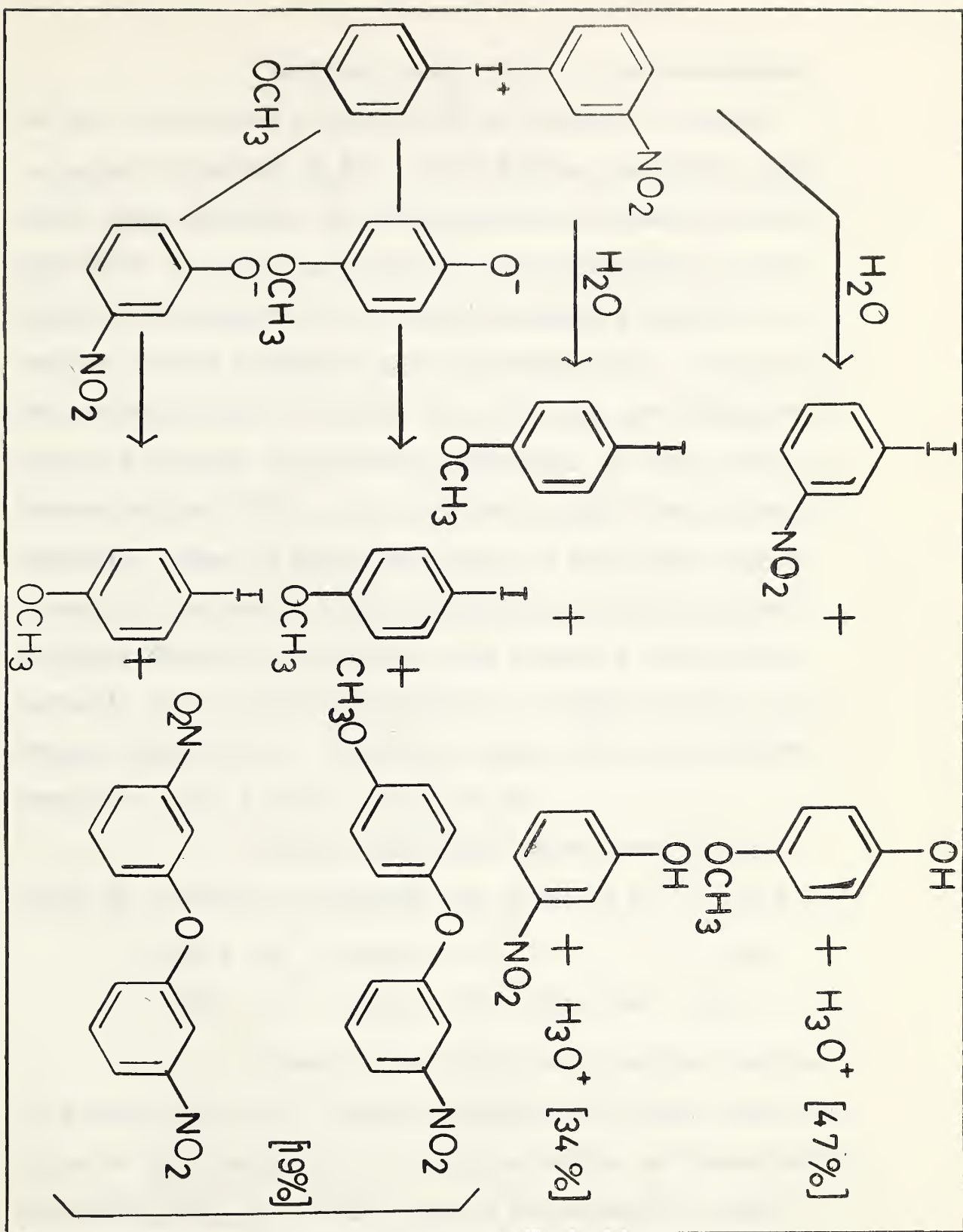
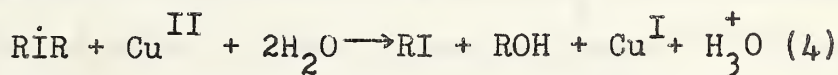
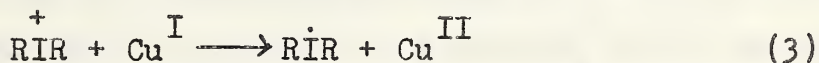


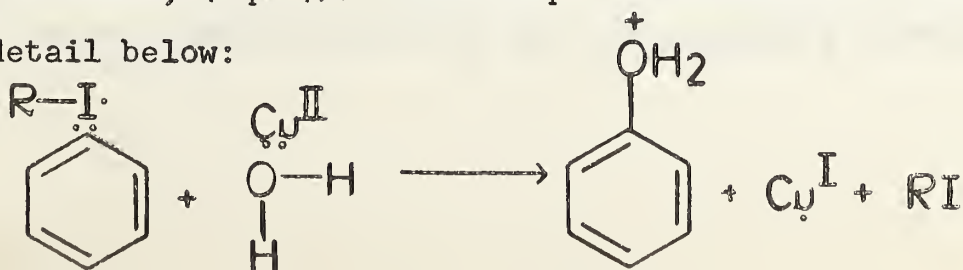
FIG. 1. Product distribution from the hydrolysis of 3-nitro-4' - methoxydiphenyliodonium ion. (J. D. Roberts and co-workers, J.Am.Chem.Soc. 81, 338 (1959).)

The first step, (eq. 1), is represented as the equilibrium formation of an unstable covalent iodonium hydroxide, R_2IOH . Such hydroxy compounds have never been isolated, but undissociated diphenyliodonium hydroxide has been suggested as an intermediate in the nonionic decomposition of diphenyliodonium chloride in aqueous sodium hydroxide with pyridine (13). By analogy, the decomposition of R_2IOH , (eq. 2), may give hydrolytic products through intermediate formation of aryl and aryl-hydroxyiodine ($RIOH$), or diaryliodine (RIR) and hydroxyl radicals. None of these radicals can have more than a transitory existence before coupling to give the final products because no products were detected which would normally arise from free radicals by dimerization or hydrogen abstraction. In effect, then, these are radical reactions with a chain length of one.

Cuprous catalyzed hydrolysis may take place by a similar mechanism, as shown in eq. 3 and 4.



Cuprous ions effect an electron transfer to iodine, (eq. 3), The diaryliodine, RIR , may then collapse to give products by a further series of one-electron transfers, (eq. 4). This step is illustrated in more detail below:

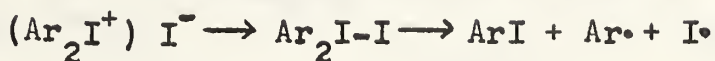


However, the sequence in time of each electron transfer is a matter of pure speculation.

Other authors have reported the possibility of radicals in iodonium salt decompositions. Irving and Reid (14) studied the photochemical decomposition of solutions of diphenyliodonium iodide in chloroform. The major products were iodobenzene, iodine, benzene and diphenyliodonium tri-iodide. It appears the reaction is autocatalytic and that the reaction rate increases as diphenyliodonium iodide dissolves in the iodobenzene formed.

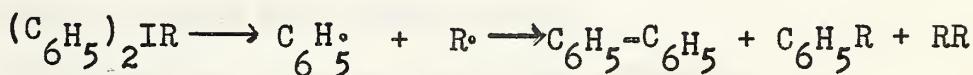
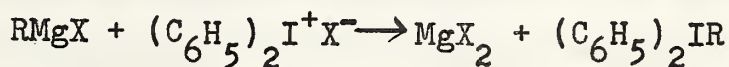
The formation of iodine and especially the formation of benzene are the most striking features which distinguish the photochemical decomposition of diphenyliodonium iodide in chloroform from its thermal decomposition. The hydrogen required for the production of benzene may be provided by the CHCl_3 or by the dehydrogenation of other aromatic groups present. Irving and Reid have not obtained direct evidence of the presence of phenyl radicals, and at the same time have not detected any by-product which could be attributed to the formation of trichloromethyl radicals. Under comparable conditions the photodecomposition of the corresponding bromides,

chlorides, or fluorides is barely detectable. This suggests that a reaction of the type

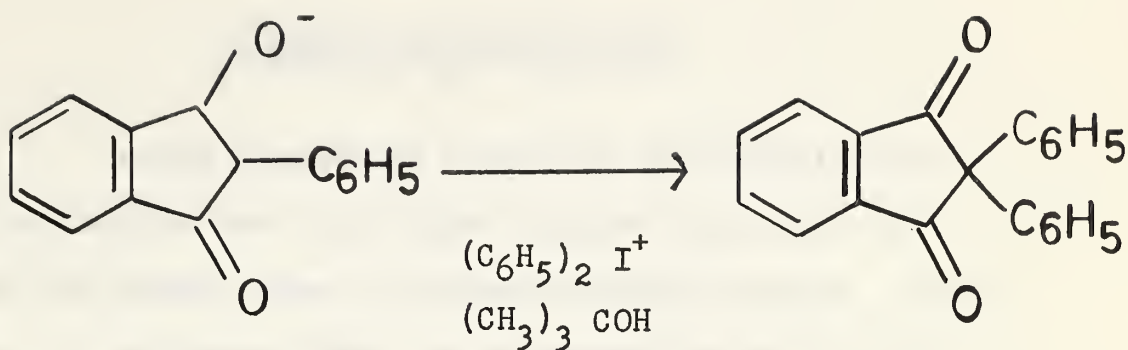


may be significant with the readily deformable iodide ions.

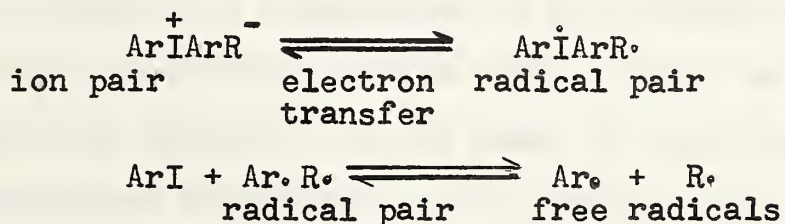
Berlinger, Dehn and Winicov (15) added dry diphenyliodonium halides to ethereal Grignard reagent near its boiling point and a fleeting yellow coloration was observed. Addition below 0° gave a yellow-orange precipitate, which lost its color on standing at room temperature. These authors propose that the variety of products obtained arises from the decomposition of tri-substituted iodines to iodo compounds and free radicals which react with each other and with the solvent.



Recently Berlinger (27) reported several reactions of the anion of 2-phenyl-1, 3-indandione with diphenyliodonium chloride and suggests the formation of free radicals as intermediates in the phenylation of carbanions.



A tentative mechanism for the phenylation of carbanions is given below.



It is proposed that electron transfer from carbanions to iodonium ions gives radical pairs. The members of such radical pairs in t-butyl alcohol largely react together, either by radical displacement of R \cdot on diphenyliodine or by coupling of R \cdot and phenyl radicals. Such free radicals couple to give ArR, ArAr and RR.

Ultraviolet spectra can give valuable information about diphenyliodonium salts. Two such studies have been undertaken (16, 17) and appear to complement each other. However, they are not in complete agreement. Ultraviolet spectra will be discussed later.

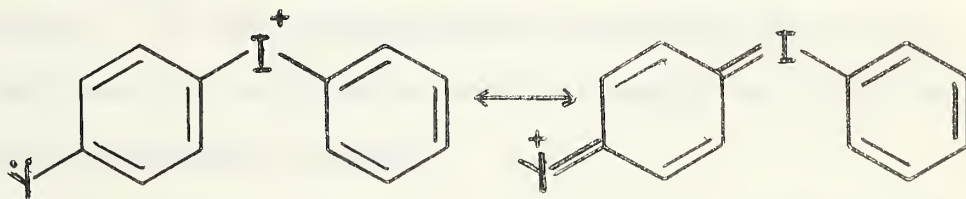
RESULTS AND DISCUSSIONS

In the literature survey of this thesis numerous references were cited that support the ionic nature of the iodine atom in diphenyliodonium cation. Some workers (4) suggested that the decomposition of an iodonium salt at least in part can decompose by way of a nonionic mechanism. It has also been reported (1) that the decomposition temperature of an iodonium salt depends upon the nature of the anion as well as the cation. Keeping the positive ion the same, it was found that the decomposition temperature of an iodonium salt varies with the nucleophilicity of the negative ion. For instance, di-o-tolyliodonium bromide decomposes at $178^{\circ}\text{C}.$, the iodide at $155^{\circ}\text{C}.$, and the sulfide at room temperature.

One might expect a lowering in decomposition temperature, as the nucleophilicity of the anion is increased. In addition the percentage of "ionic bond" would be expected to decrease. Sulfur was expected to provide such an anion. Thiophenol and some aliphatic organic sulfur compounds were considered. However the 2-naphthalenethiol derivatives because of their relative stability became very attractive for this study. Diphenyliodonium-2-naphthalenethiolate was found to be a brilliant yellow amorphous solid. As expected it decomposed in the atmosphere on rapid heating (m.p. $74-78^{\circ}$, dec.). At room

temperature it decomposed on standing for two weeks and, it decomposed with an explosive nature on grinding. In this work we propose to show that diphenyliodonium-2-naphthalenethiolate does decompose at least in part, if not completely, by a free radical mechanism.

Partial homolytic cleavage has been suggested by a number of workers (1, 4, 11, 14) for iodonium salts. An iodonium salt possesses both a positive charge and a rare gas configuration. Iodine is capable of exerting a large polarizing effect and can undergo valence shell expansion by acceptance of the electrons into a 5d (or 4f) orbital. Beringer (17) has reported evidence for such valence shell expansion beyond the octet. This process has been termed d-orbital resonance. Beringer studied the effect of functional groups on the benzene ring, and the consequences of this work will be discussed in relation to our ultraviolet spectra.

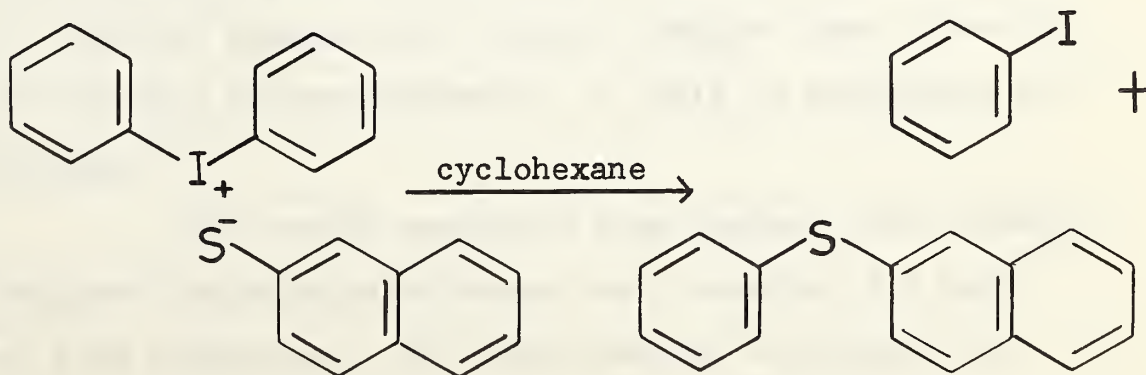


If diphenyliodonium-2-naphthalenethiolate has a covalent I-S bond, the iodine must have 10 electrons in its bonding shell. Such a covalent species would be expected to decompose by a free radical mechanism.

No attempt has been made to "trap" intermediate free radicals. Free radicals are exceedingly reactive substances, and can therefore have only a transient existence. They are so reactive that they interact with and decompose practically the first molecule they encounter, and, in consequence, the reactions which involve free radicals in solution are almost without exception reactions between free radicals and solvent molecules. By choice of solvents and by consideration of product distribution, we hope to show that neutral free radicals, as opposed to charged ions, are formed as intermediates in cyclohexane as well as in other organic solvents.

Decomposition of Diphenyliodonium-2-naphthalene-
thiolate in Cyclohexane.

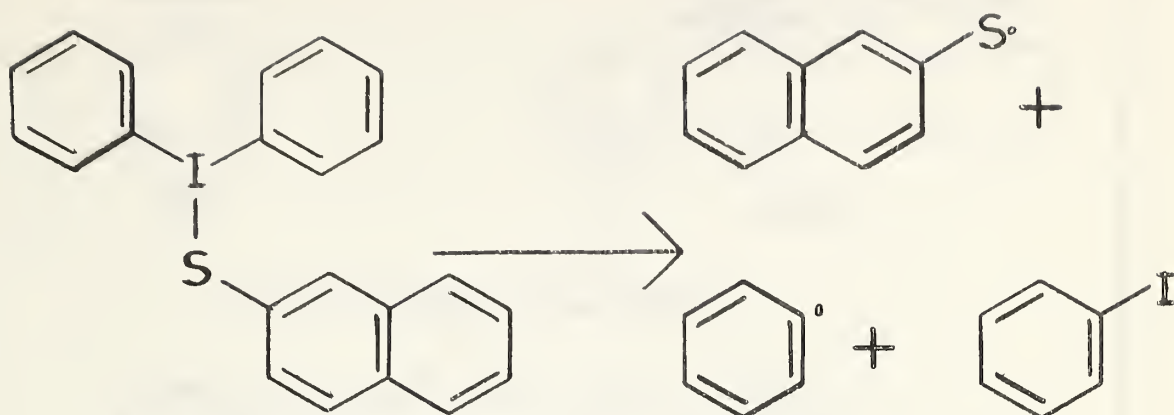
The decomposition of diphenyliodonium-2-naphthalenethiolate in cyclohexane was examined by analysis of the products. If the decomposition proceeded by an ionic mechanism then the only major products would be iodobenzene and phenyl-2-naphthyl sulfide.



Both products should be formed in high yields, which was not the case. For an ionic decomposition the starting material would have to possess the rare gas configuration and would have the positive charge on the iodine. The first step then would be dissociation into the anion and cation followed by C-I bond cleavage. The naphthalenethiolate anion either simultaneously or later would attack the positive charge on the benzene ring. Because cyclohexane is not a good solvent for dissociation of the starting material, the idea of an ionic mechanism in this case is not attractive.

A much more plausible scheme assumes that the I-S bond of diphenyliodonium-2-naphthalenethiolate has covalent character. This requires the iodine atom to have 10 electrons in its outer shell. The idea of iodine expanding its octet has received much attention in the literature (19-21), and iodine with a 10 electron outer shell is acceptable. If the anion and cation both have appreciably distorted electron clouds, then the compound would possess some covalent bond character. Although the I-S bond may possess only partial covalent bond character, for the ease of representation, it will be considered as covalent.

Our second mechanism then assumes that diphenyliodonium-2-naphthalenethiolate has a covalent I-S bond, and that furthermore, the photochemical decomposition occurs via free radicals.



The intermediate free radicals react instantaneously to form a large number of products. The possible compounds from a decomposition are listed in Fig. 2. The actual product distribution found is recorded in Fig. 3.

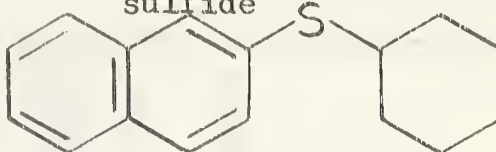
Iodobenzene is formed in essentially quantitative yield. A considerable quantity of benzene is formed, and this product cannot be accounted for by an ionic mechanism. A free radical mechanism permits the formation of phenyl radicals which then can react in a number of ways. First, phenyl radicals can couple to form biphenyl. Second, the phenyl radicals can abstract hydrogen from the solvent, cyclohexane, to give benzene and cyclohexyl radicals. Third, phenyl radicals might couple with cyclohexyl radicals to form cyclohexylbenzene. The first and third steps are unlikely due to the high reactivity of phenyl and cyclohexyl radicals. Step two is consistent with the formation of benzene in the product distribution. 2-Naphthalenethio-

benzene



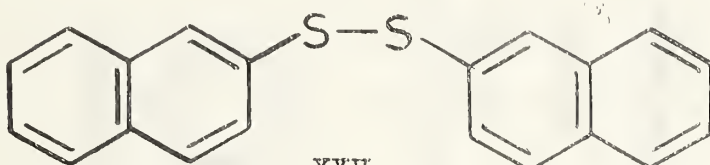
XXIV

cyclohexyl-2-naphthyl sulfide



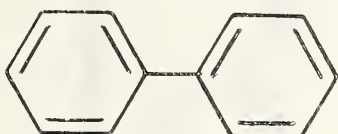
XXVI

2,2'-dinaphthyl disulfide



XXV

biphenyl



XXVIII

cyclohexylbenzene



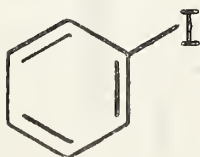
XXIX

dicyclohexyl



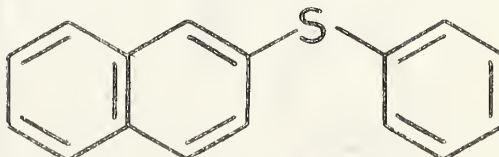
XXX

iodobenzene



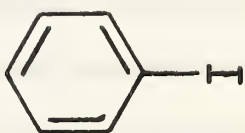
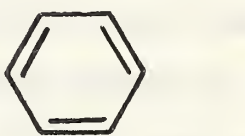
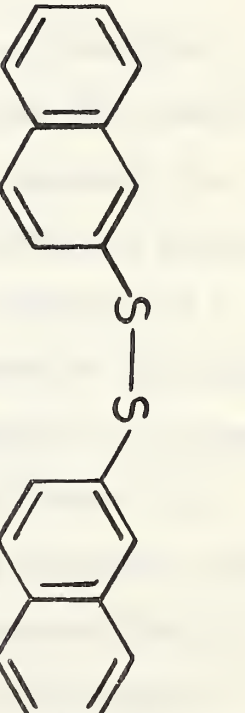
XXIII

phenyl-2-naphthyl sulfide



XXVII

FIG. 2. The possible products from a free radical decomposition of diphenyliodonium-2-naphthalenethiolate in cyclohexane.

PRODUCT			
YIELD	99 ± 2%	30 ± 1.5%	24.1%
METHOD OF SEPARATION	V.P.C.	V.P.C.	gravimetric

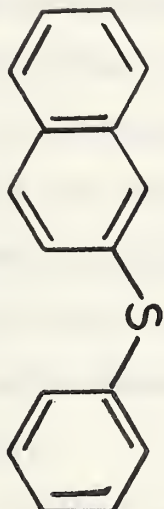
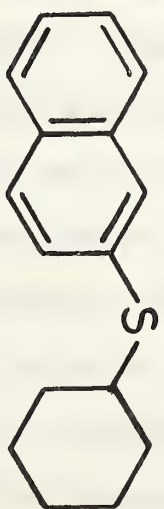
PRODUCT		
YIELD	32% (combined)	
METHOD OF SEPARATION	vacuum distillation	

FIG. 3. Decomposition products of diphenyliodonium-2-naphthalenethiolate in cyclohexane.

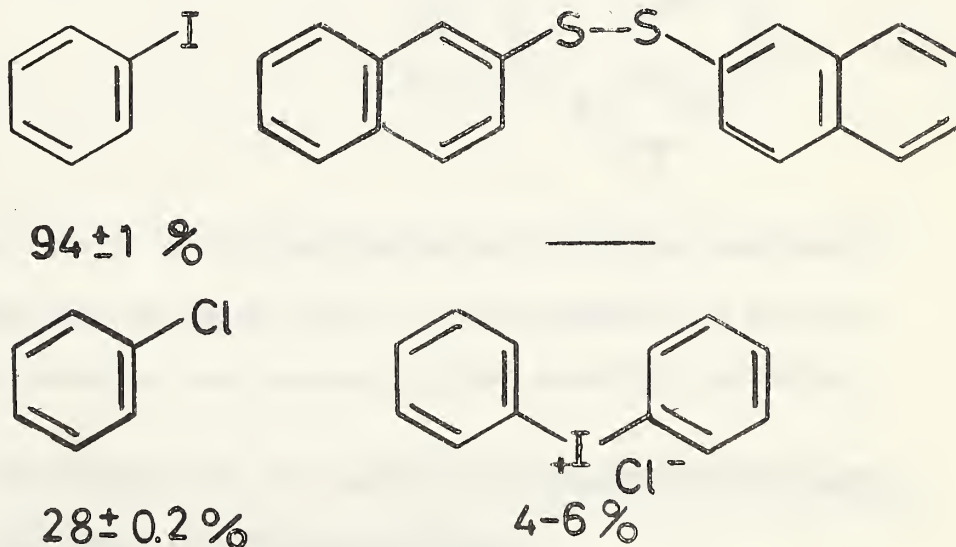
2-naphthalenethiolate radicals to give phenyl-2-naphthyl sulfide, cyclohexyl-2-naphthyl sulfide and 2,2'-dinaphthyl disulfide respectively and were shown to be present. Biphenyl, cyclohexylbenzene and dicyclohexyl were not detected in the reaction mixture, and therefore, were either not present or were formed in very small quantities. This is to be expected because phenyl and cyclohexyl radicals are too short lived to remain in solution long enough to couple with one another. The formation of 2,2'-dinaphthyl disulfide can only be explained by a free radical mechanism. Aromatic sulfide free radicals are much less reactive radicals (22), and presumably are stable enough to couple with each other as well as with phenyl and cyclohexyl radicals.

Phenyl-2-naphthyl sulfide and cyclohexyl-2-naphthyl sulfide were recovered in a combined 32% yield. Since an adequate separation of these two compounds required repeated distillations, it was difficult to determine the exact amount of each component. Analyses of a mixture by integrated nuclear magnetic resonance spectrum and the measurement of intensities of aliphatic vs. aromatic hydrogen peaks in the infrared spectrum showed the binary mixture was mostly phenyl-2-naphthyl sulfide. We interpret all of these results, for the decomposition of diphenyliodonium-2-naphthalenethiolate in cyclohexane, as evidence for a free radical decomposition mechanism.

Decomposition of Diphenyliodonium-2-naphthalene-
thiolate in Carbon Tetrachloride.

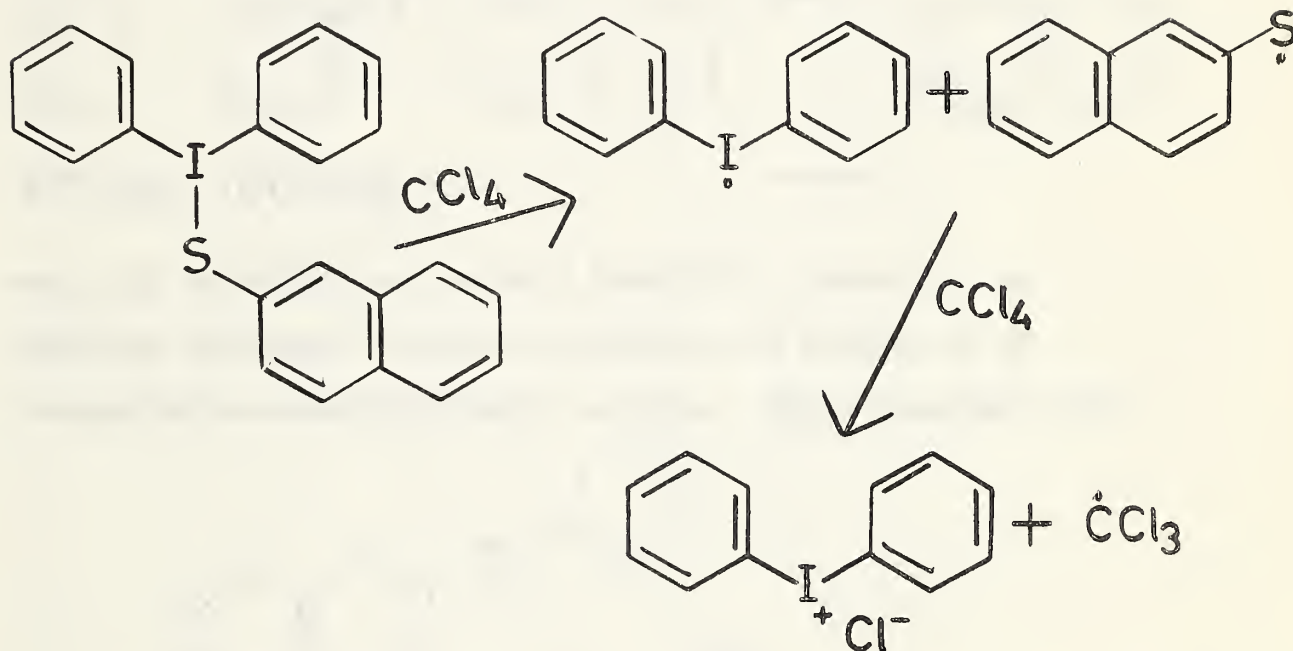
The results obtained from the decomposition of diphenyliodonium-2-naphthalenethiolate in carbon tetrachloride are not consistent with an ionic mechanism. The major products from a heterolytic cleavage would be iodobenzene and phenyl-2-naphthyl sulfide.

Although all the products were not identified, the identified products strongly support a homolytic cleavage. Attempts to ascertain the formation of 2-naphthalene sulfonyl chloride were unsuccessful. However, aromatic sulfonyl chlorides are reported to be extremely unstable (23). The products that were isolated are given below:



The formation of chlorobenzene was especially encouraging because this product can readily be explained by abstraction of a chlorine atom from the solvent. It appears highly improbable to us that carbon tetrachloride

would undergo a nucleophilic attack on the positively charged phenyl ring. The formation of both 2,2'-dinaphthyl disulfide and diphenyliodonium chloride are compatible with a free radical decomposition mechanism. The formation of diphenyliodonium chloride in low yield is pictured in following scheme:



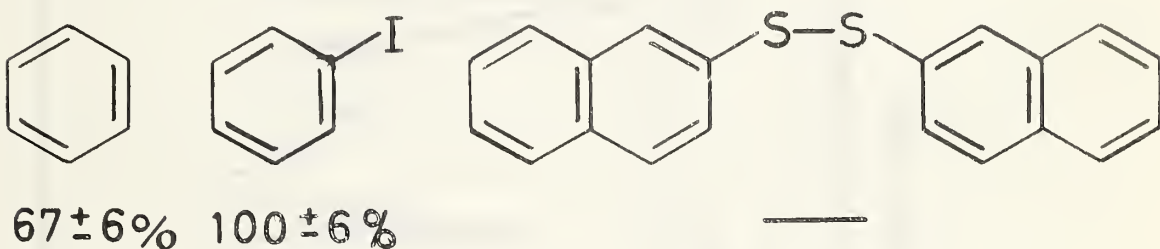
Although the yield of diphenyliodonium chloride was small (4-6%), there was no doubt that it was present in the decomposition products and absent in the starting material.

Decomposition of Diphenyliodonium-2-naphthalenethiolate in Tetrahydrofuran.

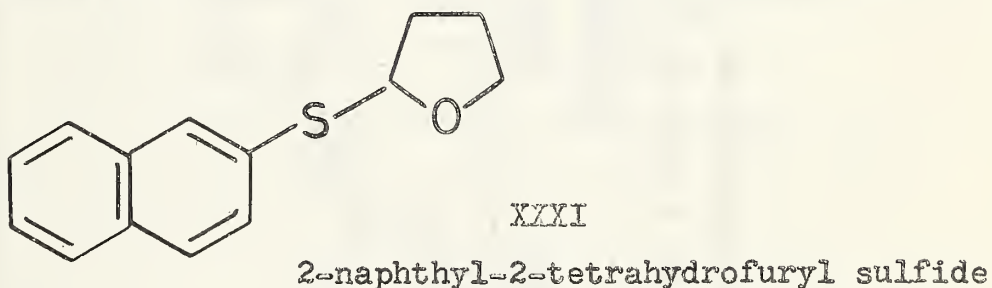
The decomposition of diphenyliodonium-2-naphthalenethiolate was carried out in peroxide free tetrahydrofuran under dry nitrogen. As in other solvents, sunlight or ultraviolet light greatly accelerated the

decomposition. The expected products for heterolytic cleavage are similar for cyclohexane, carbon tetrachloride and tetrahydrofuran.

As in the case of cyclohexane and carbon tetrachloride, formation of the following products



can only be consistent with a homolytic cleavage. In addition secondary evidence supports the formation of 2-naphthyl-2-tetrahydrofuryl sulfide. This compound could



not be isolated in pure form. Analysis for the impure material showed it to contain 13.1% sulfur (calc. 13.9%). The material did not give a sharp nuclear magnetic resonance spectrum. The presence of 2-naphthyl-2-tetrahydrofuryl sulfide is based mainly on the infrared spectrum.

The peaks at 3050 cm^{-1} , 2972 cm^{-1} , 2945 cm^{-1} and 2865 cm^{-1} have been assigned to carbon-hydrogen stretching frequencies. The naphthalene skeletal vibrations

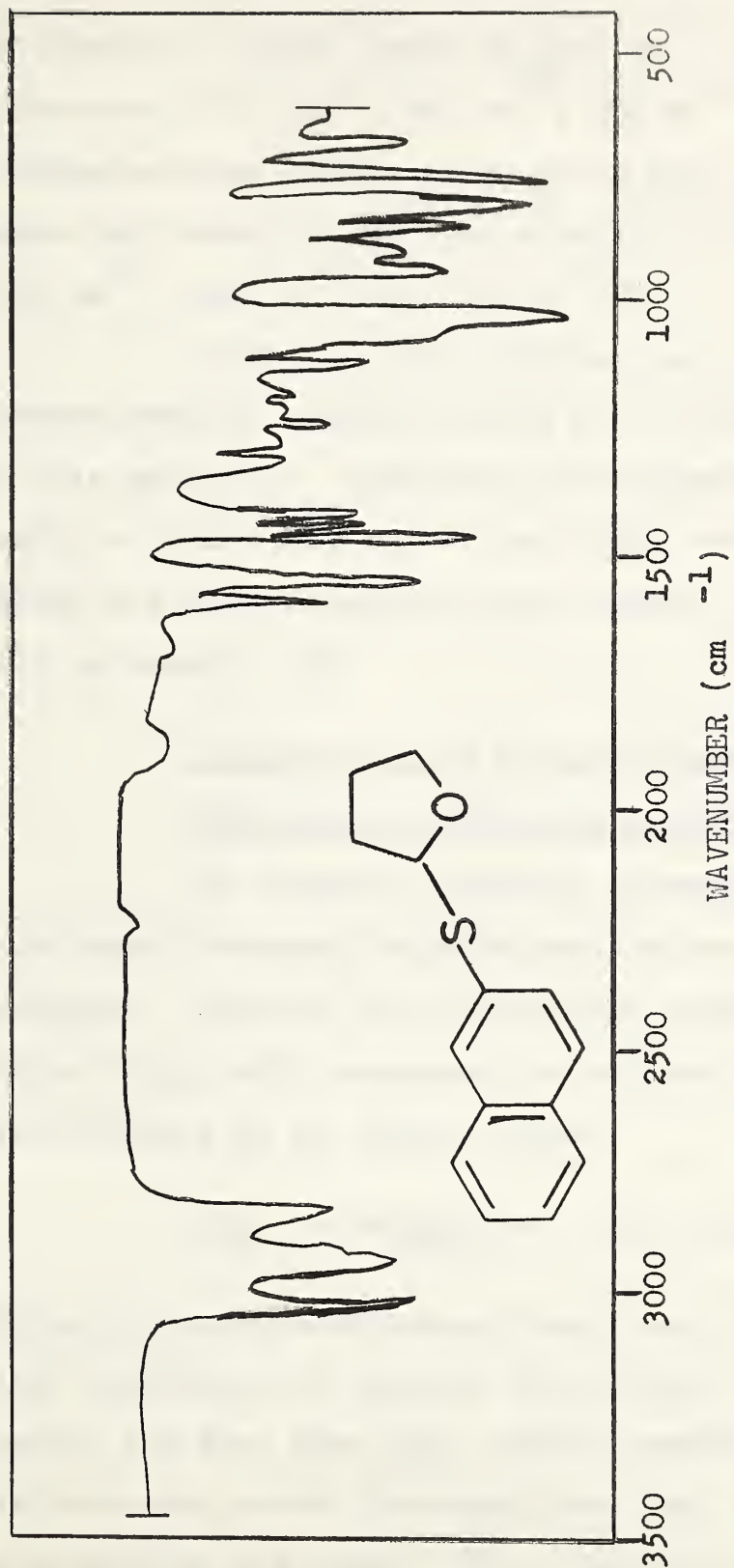


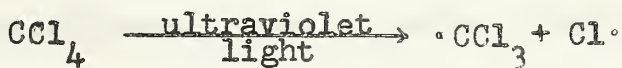
FIG. 4. Infrared spectrum of a film of 2-naphthyl-2-tetrahydrofuryl sulfide showing the region 3500-600 cm⁻¹. (Perkin Elmer 221)

occur at 1622 cm^{-1} and 1498 cm^{-1} . An intense absorption attributed to C=O-C occurs at 1043 cm^{-1} , and C-H deformations are at 890 cm^{-1} , 845 cm^{-1} , 806 cm^{-1} and 735 cm^{-1} . Tetrahydrofuran absorbs strongly at 1076 cm^{-1} and also has bands very close to and corresponding to those found at 2972 cm^{-1} , 2945 cm^{-1} and 2865 cm^{-1} (24).

Attempts to make derivatives of 2-naphthyl-2-tetrahydrofuryl sulfide failed due to the decomposition of this material. 2-Naphthyl-2-tetrahydrofuryl sulfide is really a cyclic thio-acetal and while not many such compounds are known, they are very unstable especially if acid is present (25).

Decomposition of Diphenyliodonium-p-toluene-sulfonate in Carbon Tetrachloride.

The evidence presented supports decomposition of diphenyliodonium-2-naphthalenethiolate by free radical mechanism. However, the possibility exists that ultraviolet light might decompose the solvent thus initiating free radicals in the manner shown.

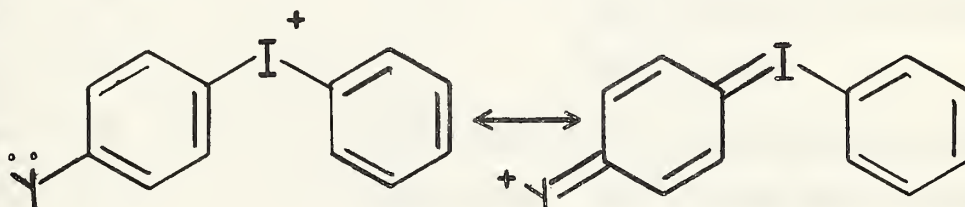


Diphenyliodonium-p-toluenesulfonate was treated under identical conditions in chloride free carbon tetrachloride. Despite the fact that this control compound was treated for twice the normal decomposition time, no evidence of decomposition was found. The crystalline solid was recovered

without loss in weight. Both the diphenyliodonium-p-tosylate and carbon tetrachloride gave negative chloride ion tests.

Ultraviolet Spectra of Diaryliodonium Salts.

Beringer (17) used ultraviolet spectra to demonstrate d-orbital resonance. This is the process whereby iodine and other elements below the first row in the periodic table can interact with adjacent unbonded electrons by expansion of their valence shells beyond the octet.



These workers (17) found a striking similarity between the ultraviolet absorption spectrum of iodobenzene and that of the diphenyliodonium cation. Both have similar maxima at 226 mμ and 207 mμ, and the latter band was assigned to the benzenoid absorption (Table I).

The molar extinction coefficient of the 209 mμ band of the diphenyliodonium cation ($\log \epsilon 4.23$) is slightly more than double that of the 207 mμ band ($\log \epsilon 3.86$) of iodobenzene, while the 226 mμ band common to both is of about the same intensity. The additivity of absorption ascribable to the benzene ring and the lack of shift in the 226 mμ band in the diphenyliodonium cation is consistent with the picture of benzene rings which are separated

TABLE I

Ultraviolet Absorption Maxima of Benzene and
Substituted Iodobenzenes.

Compound	A-Band m μ (log ϵ)	B-Band m μ (log ϵ)	C-Band m μ (log ϵ)
benzene	203 (3.87)	-	255 (2.31)
iodobenzene	207 (3.86)	226 (4.12)	257 (2.85)
2-NO ₂ -	"	260 (3.54)	310 (3.18)
3-NO ₂ -	"	260 (3.81)	315 (3.00)
4-NO ₂ -	"	294 (4.07)	-
4-OCH ₃ -	"	209 (3.89)	233 (4.30) 280 (3.15)
2-NH ₂ -	"	213 (4.36)	238 (3.89) 293 (3.42)
3-NH ₂ -	"	217 (4.31)	243 (3.86) 297 (3.29)
4-NH ₂ -	"	211 (4.04)	248 (4.22) 298 (3.24)
4-OH-	"	210 (4.32)	246 (4.12) -

Data from F. M. Beringer and co-workers, J. Am.
Chem. Soc. 82, 5136 (1960).

TABLE II

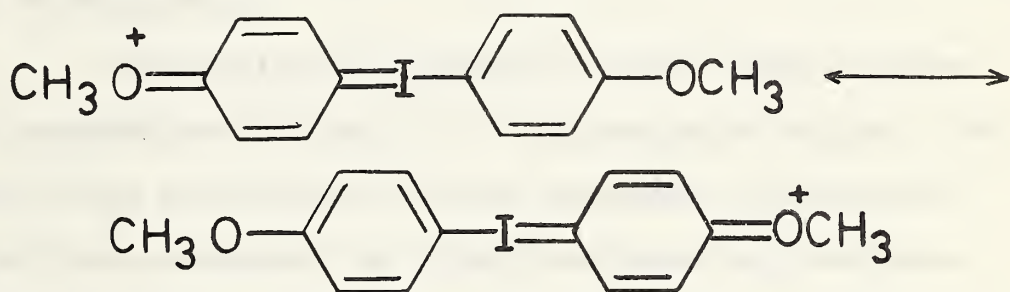
Ultraviolet Absorption Maxima of Substituted
Diphenyliodonium Salts.

Substituents	A-Band m μ (log ϵ)	B-Band m μ (log ϵ)	C-Band m μ (log ϵ)
3-CH ₃ O-	210 (4.39)	218 (4.38)	298 (3.34)
4-CH ₃ O-	210 (4.28)	245 (4.16)	-
4,4'-(CH ₃ O) ₂ -	209 (4.32)	252 (4.29)	-
2-NO ₂ -	210 (3.94)	260 (3.82)	-
3-NO ₂ -	217 (4.05)	248 (4.02)	-
4-NO ₂ -	209 (4.05)	251 (4.14)	-
2-NH ₂ -	214 (4.40)	222 (4.42)	323 (3.23)
3-NH ₂ -	211 (4.02)	226 (4.37)	313 (3.26)
4-NH ₂ -	211 (3.79)	285 (4.03)	-
4,4'-(NH ₂) ₂ -	-	288 (4.21)	-
4,4'-(NO ₂) ₂ -	220 (4.06)	260 (3.83)	-
3-NO ₂ -4'-NH ₂ -	210 (4.43)	240 (4.20)	-
		286 (4.06)	
4-NO ₂ -4'-NH ₂ -	210 (4.40)	248 (4.30)	-
		295 (4.12)	
4-OH	210 (4.32)	246 (4.12)	-
4,4'-(OH) ₂ -	211 (4.42)	254 (4.26)	-

Data from: F. M. Beringer and co-workers,
J. Am. Chem. Soc. 82, 5137 (1960).

by an insulator and not in conjugation.

When a comparison is made of the B-bands of diphenyliodonium ions with electron donating p-substituents (Table II), a bathochromic shift is seen which parallels the order of electron releasing ability of the substituents. The wave length increments between the B-bands of the iodoaromatic compounds and the corresponding iodonium cations increase with the electron-releasing power of the substituents, being most prominent for the anilines and phenoxides. The significant increase in λ_{max} in going from the monosubstituted to the disubstituted diphenyliodonium cations (viz. 4-methoxy vs. 4,4'-dimethoxy) suggests an increase in the length of the conjugated system, i.e.

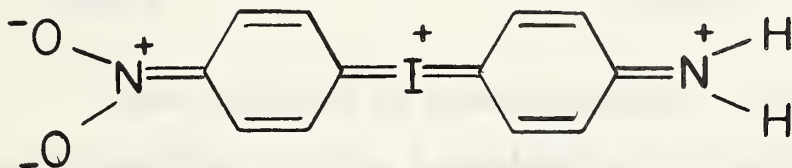


These observations lend support to the concept of iodonium participation in conjugation in the excited state.

With the establishment of the idea of iodonium-substituent interaction, a comparison between 3- and 4-nitro-4'-aminodiphenyliodonium cations were made (Table II). Not only are all the bands at longer wave length in the 4-nitro isomer, but they are more intense. The 285 mμ band of the 4-aminodiphenyliodonium cation

has moved to 295 mμ in the 4-nitro isomer. The bands at 240 and 248 mμ in the 3- and 4-nitro isomers respectively, can be identified with the nitro bands at 248 and 251 mμ in the 3- and 4-nitrodiphenyliodonium cations.

This data points to conjugation between the nitro and amino groups which must be through the iodonium atom.

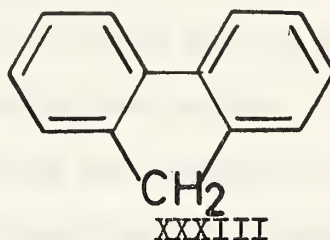
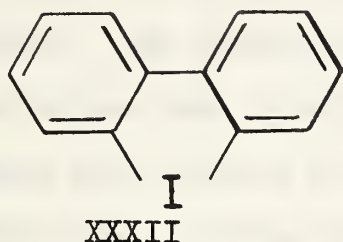


Such interaction occurs when electronically complementary groups such as nitro and amino are in the 4,4' -positions. However, this through-conjugation is of a relatively low order of magnitude.

Originally we planned to study diphenyliodonium-2-naphthalenethiolate in the ultraviolet region. Because of the instability of this compound, ultraviolet studies were performed on dibenziodolium-2-naphthalenethiolate in collaboration with J. W. Greidanus of this laboratory.

Irving, Turner and Reid (16) report that the spectrum of dibenziodolium ion proved to be little effected by the nature of the anion. It showed a remarkable similarity to that of fluorene closer indeed than that of diphenyliodonium ion to biphenyl. This similarity is expected

because there is now direct conjugation between the two benzene rings in both XXXII and XXXIII and the geometry of the fused 5- and 6-membered rings should be similar.



The spectrum of dibenziiodolium cation, XXXII, has been reported to have a maximum at 263 mμ and a shoulder at 217 mμ (16). We have examined dibenziiodolium chloride and dibenziiodolium-p-toluenesulfonate, and our results are in agreement with these values. The chloride has a maximum at 263 mμ (log ε 3.41) and shoulders at 223 and 216 mμ (Fig. 5). The tosylate also has a maximum at 263 mμ (log ε 4.11) with a shoulder at 217 mμ.

The ultraviolet absorption spectra of 2-naphthalenethiol in 95% ethanol with and without 0.01N sodium hydroxide has been published (26). Our results are shown (Fig. 6) and these spectra are almost superimposable with those reported. 2-Naphthalenethiol absorbs at 292 mμ (log ε 3.88), 283 mμ (log ε 4.00), 272 mμ (log ε 3.94), 240 mμ (log ε 4.60) and 212 mμ (log ε 4.58). 2-Naphthalenethiolate has maxima at 306 mμ (log ε 4.35), 293 mμ, 263 mμ (log ε 4.77) and 216 mμ (log ε 4.86).

Irving, Turner and Reid (16) have shown that the

ultraviolet spectra of diphenyliodonium and dibenziodolium cations are little effected by the nature of the anion. If dibenziodolium-2-naphthalenethiolate does possess an "ionic" I-S bond, then the anion and cation should have little or no effect on the ultraviolet spectra of each other. The result should be the sum of the dibenziodolium cation and the 2-naphthalenethiolate anion. Since both of these ions absorb very strongly at exactly 263 m μ , the ultraviolet spectrum of dibenziodolium-2-naphthalenethiolate should have a maximum at or very close to 263 m μ .

Indeed, no such maximum was found at 263 m μ (Fig. 7). The spectrum shows continuous absorption from 290 to 214 m μ with a shoulder at 249 m μ . The intensities have little significance, since this compound is almost insoluble in 95% ethanol. Moreover, the spectrum was not due to the decomposition products which have a different ultraviolet spectrum (Fig. 8). In dimethyl sulfoxide dibenziodolium-2-naphthalenethiolate has a maximum at 364 m μ ($\log \epsilon$ 4.00) which is not shown by the tosylate in dimethyl sulfoxide. We interpret these results as spectral evidence in support of a covalent I-S bond in dibenziodolium-2-naphthalenethiolate.



FIG. 5. Ultraviolet absorption spectrum of dibenziodolium chloride in 95% ethanol (0.0670 g./liter, 1 cm. cell Beckman DK-2).

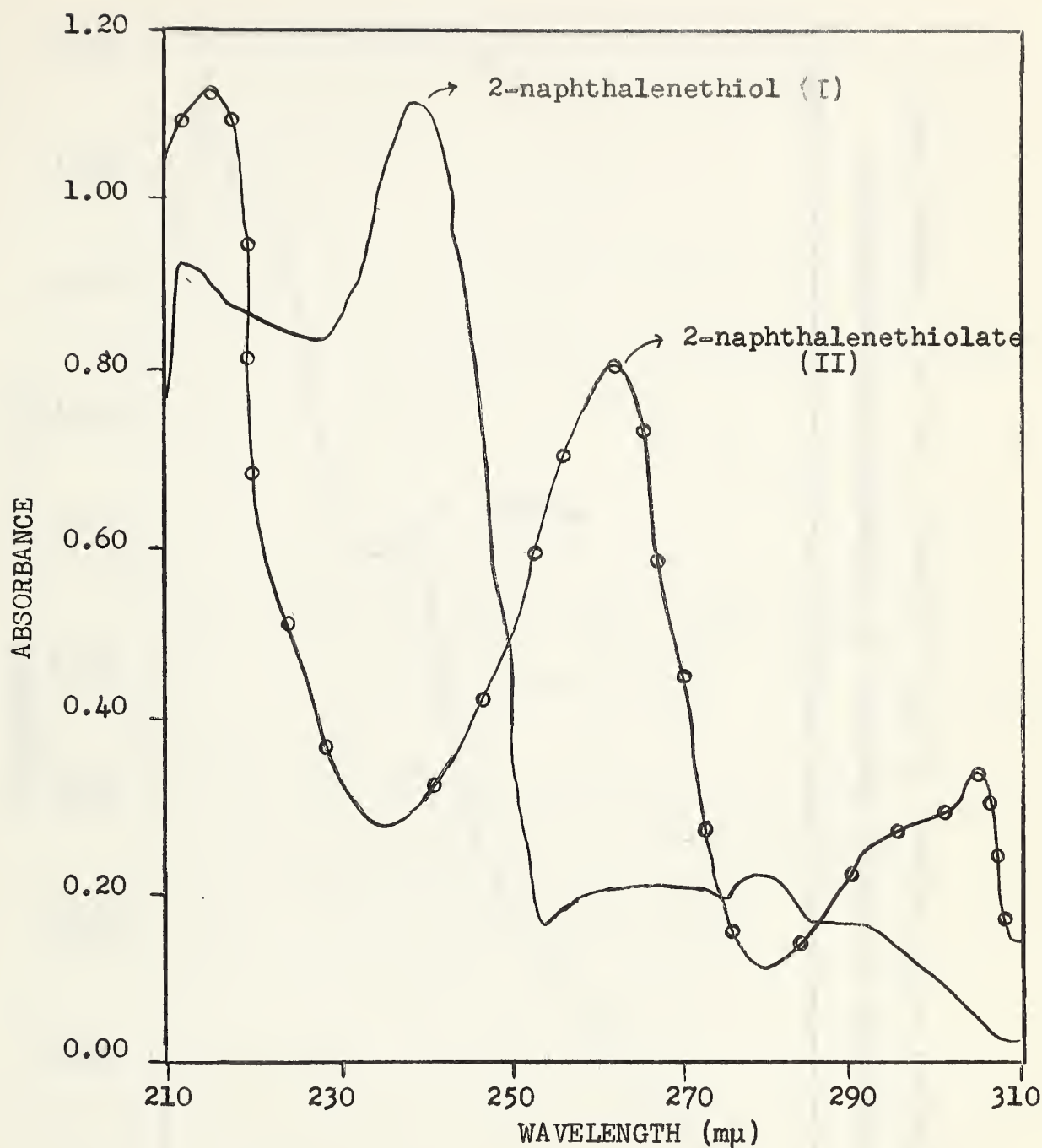


FIG. 6. Ultraviolet absorption spectra of 2-naphthalene-
thiol (I) and 2-naphthalenethiolate (II) in 95%
ethanol. (I 0.0400 g./liter, 0.1 cm. cell,
Beckman DK-2; II 0.0025 g./liter, 1 cm. cell,
Beckman DK-2).

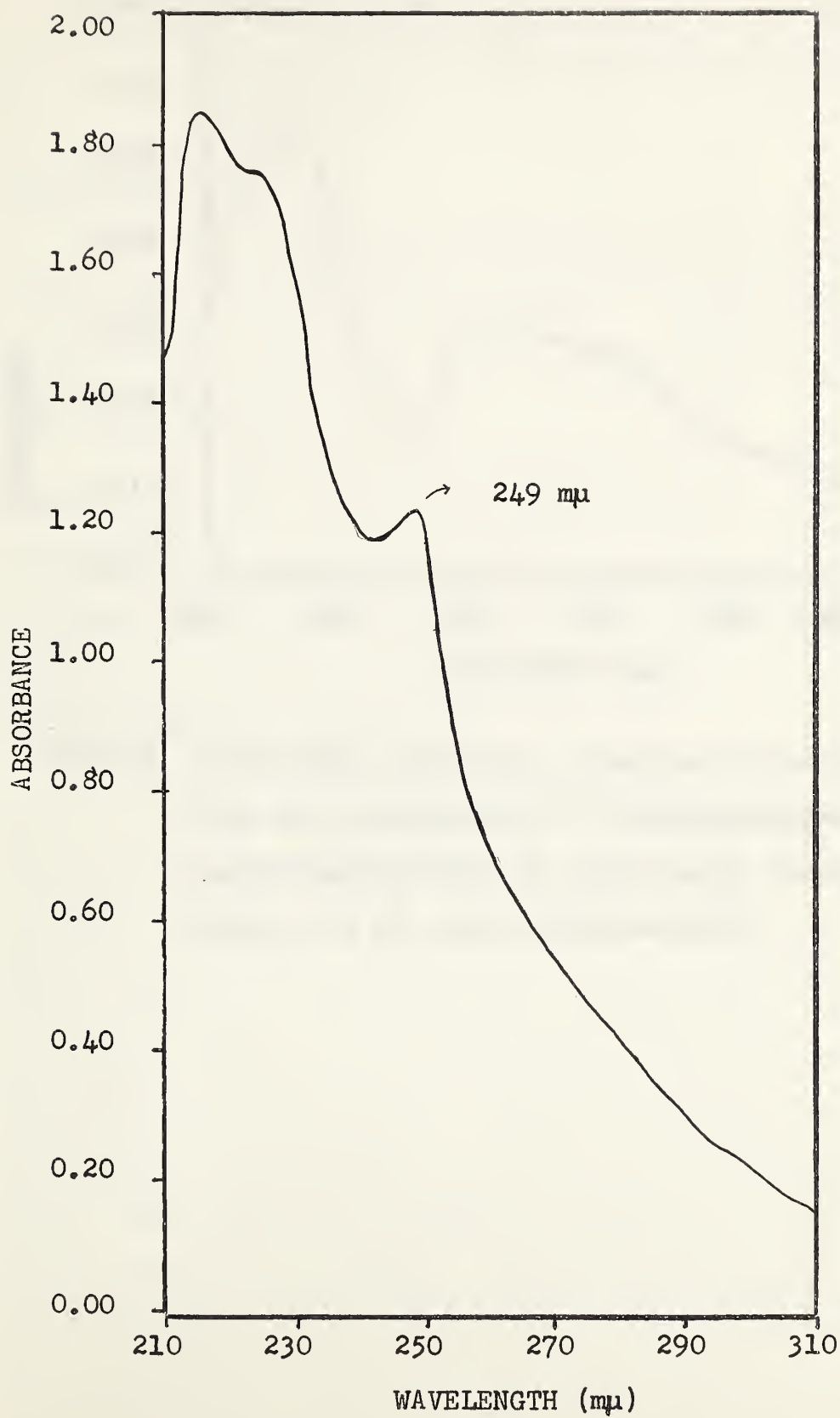


FIG. 7. Ultraviolet absorption spectrum of dibenziodolium-2-naphthalene-thiolate in 95% ethanol (0.0100 g./liter, 1 cm. cell, Beckman DK-2).

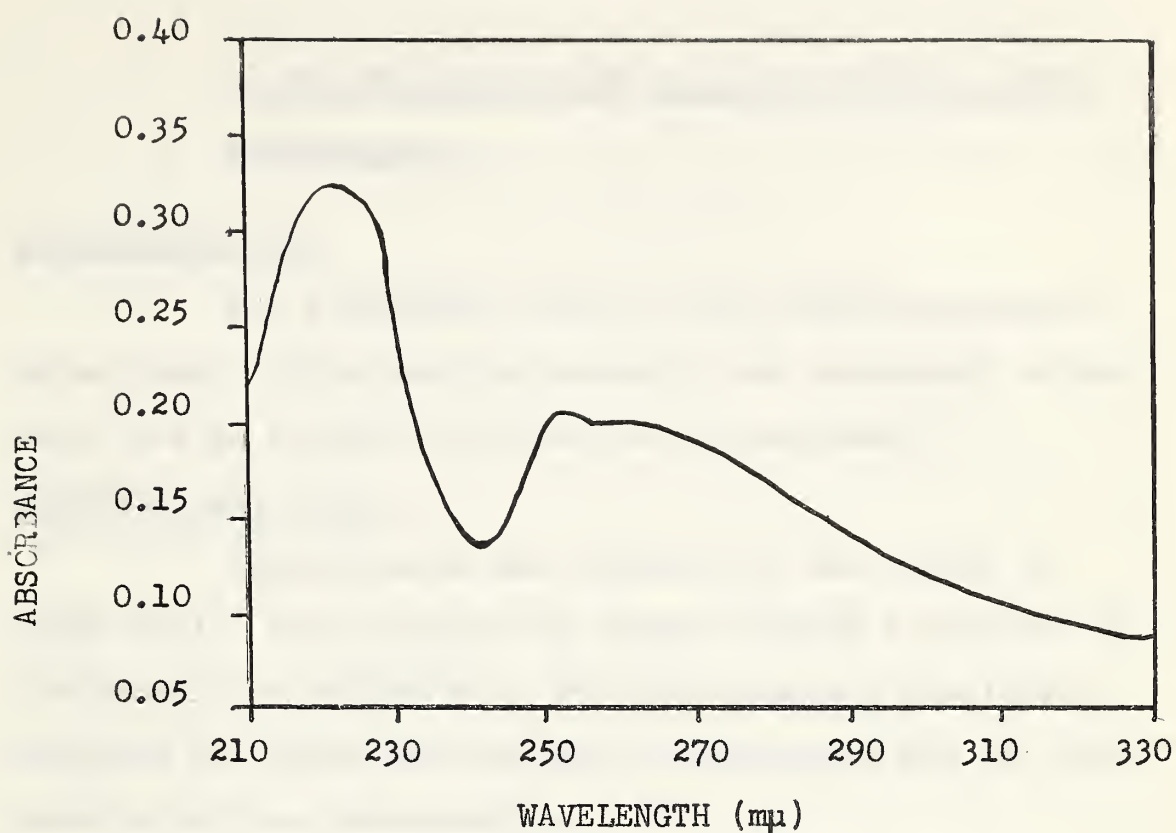


FIG. 8. Ultraviolet absorption spectrum of the products from the decomposition of dibenziodolium-2-naphthalenethiolate in 95% ethanol (0.0100 g./liter, 0.1 cm. cell, Beckman DK-2).

EXPERIMENTAL SECTION

1. The Preparation of Diphenyliodonium Iodide Derivatives.

Iodobenzene (I).

The iodobenzene used in this work was Eastman white label. This starting material was completely colorless, and no further purification was performed.

Iodosobenzene (III).

Iodosobenzene was prepared by the method of Lucas (28). Dry chlorine was passed through a solution of iodobenzene in chloroform. The iodosobenzene dichloride obtained was quite pure and was used directly for the preparation of the iodosobenzene.

Diphenyliodonium Iodide (IV).

The preparation of diphenyliodonium iodide was a variation of Beringer's procedure (9). To a cold solution of iodosobenzene (5.0 g., 0.0227 mole), benzene (12.5 ml.), glacial acetic acid (65 ml.) and acetic anhydride (12.5 ml.), there was added dropwise with stirring sulfuric acid (5.0 ml.). After 24 hours the reaction mixture was diluted with water (100 ml.), extracted twice with ether, shaken with activated carbon (5 g.), and filtered. The addition of potassium iodide (8.05 g.) previously dissolved in water, afforded the iodonium iodide. The solid was collected, washed with water, then with acetone, and dried to give a cream-colored diphenyliodonium

iodide. The yield was 62%.

Diphenyliodonium Chloride (VI).

Diphenyliodonium chloride was prepared by the method of Beringer (9). After repeated washings with acetone and recrystallization from water this material melted at 227-228^o dec. (lit. (9), 227-228^o).

Diphenyliodonium-2-naphthalenethiolate (VII).

Diphenyliodonium chloride (5.0 g.) was dissolved in 2 liters of cold distilled water. In a separate flask 2-naphthalenethiol, Eastman white label, was dissolved in a slight excess of dilute sodium hydroxide. After most of the solid went into solution the liquid was rapidly filtered into the diphenyliodonium solution. Every precaution was taken to prevent the formation of 2,2' -dinaphthyl disulfide. Since this was formed at the surface of the liquid, the bottom of the funnel was kept below the surface of the liquid.

After the addition was complete more water was added and on rapid stirring with a glass rod the solid began to coagulate. Most of the liquid could be decanted. The washing of the product by decantation was repeated about ten times or until the supernate was clear. The brilliant yellow solid was collected on a Buchner funnel and washed exhaustively with water. The diphenyliodonium-2-naphthalenethiolate was thoroughly dried under vacuum. The chunks were cautiously broken up and stored at 5^o. This compound is very sensitive to shock or grinding and

several times flashed into an orange flame with dark smoke.

The yield was 4.9 g. (71%), m.p. 74-78° dec..

Anal. Calcd. for $C_{22}H_{17}IS$: I, 28.84; S, 7.29.

Found: I, 28.31, 28.49; S, 7.66.

Diphenyliodonium-p-toluenesulfonate (VIII).

Equimolar quantities of p-toluenesulfonic acid and diphenyliodonium chloride were dissolved in the minimum volume of dilute sodium hydroxide. Excess p-toluenesulfonic acid was added to provide a common-ion effect. Compound VIII crystallized from the solution, m.p. 179-181°. Beringer (29) prepared diphenyliodonium-p-toluenesulfonate by metathesis of iodonium halides with the soluble lead salt of the p-toluenesulfonic acid in 69% yield, m.p. 178-181°.

2. Decomposition of Diphenyliodonium-2-naphthalenethiolate (VII).

Irradiation of Diphenyliodonium-2-naphthalenethiolate in Cyclohexane.

Diphenyliodonium-2-naphthalenethiolate (9.66 g.) was added to a standard taper round-bottomed flask (500 ml.), and cyclohexane (100 ml.) was added. The air was removed by use of dry nitrogen, and the flask was stoppered. The mixture was irradiated by ultraviolet light with agitation in a wrist-action shaker. After five days more cyclohexane (100 ml.) was added, and the decomposition continued for one more day. Almost all of the yellow solid disappeared.

The cloudy solution was filtered. The precipitate (0.1 g.) was insoluble in water and was mostly starting material. The filtrate was evaporated to a small volume (20 ml.) and filtered, and afforded a solid which was washed with a small amount of fresh cold cyclohexane. The precipitate weighed 0.59 g., m.p. 125-133°. The filtrate was evaporated to a brown oil (10 ml.), which was dried in a vacuum desiccator for one day. This oil was taken up in methanol (20 ml.) and filtered, and afforded a solid which weighed 0.25 g., m.p. 105-120°.

The melting point of a mixture of each solid with pure 2,2'-dinaphthyl disulfide and the infrared spectra showed both of these solids were 2,2'-dinaphthyl disulfide. The overall yield was 24.1%.

Under similar conditions diphenyliodonium-2-naphthalenethiolate (0.924 g.) was decomposed in cyclohexane (20 ml.). To the reaction product was added bromobenzene (1 millimole, 0.1685 g.), which was used as an internal standard for gas-liquid chromatography. About 2 ml. of the solution were rapidly filtered, and the filter paper was washed with a few drops of acetone. The clear yellow filtrate was now ready for gas-liquid chromatography. All analyses were performed on a Perkin Elmer Model 154D Vapor Fractometer. Benzene and iodobenzene were found to be present (Table III).

In an identical manner diphenyliodonium-2-naphthalenethiolate (10.0 g.) was decomposed in cyclohexane

(473 ml.). After two days the reaction was complete and was filtered. The filtrate was evaporated to a yellow oil. This was extracted with 3-8 ml. portions of cold ethanol and filtered. The dried precipitate was mostly 2,2' -dinaphthyl disulfide. The filtrate was again evaporated and the resulting brown oil was vacuum distilled. Three fractions were collected.

FRACTION	TEMPERATURE	PRESSURE	WEIGHT
0	26-148 ^o	0.5 mm.	trace
1	152-154 ^o	"	1.56 g.
2	155-160 ^o	"	0.21 g.

The infrared spectra of both fractions (1 & 2) were identical. The fractions were combined and solidified at 5^o.

Some of the solid material (0.8 g.) was dissolved in a small volume of cold methanol, decolorized and filtered.

TABLE III

Quantitative Gas-liquid Chromatography

Analyses for Volatile Products in the Decomposition of
Diphenyliodonium-2-naphthalenethiolate in Cyclohexane.

Sample No.	Retention time (sec.)	Substance	Peak height	Half width	Area	Yield (millimoles)
1.	308	bromobenzene	25.6	0.53	13.57	1.0732
	581	iodobenzene	28.2	0.95	26.79	2.05
2.	310	bromobenzene	30.2	0.55	16.61	1.0732
	585	iodobenzene	33.4	0.95	31.73	2.12
3.	309	bromobenzene	26.7	0.53	14.14	1.0732
	587	iodobenzene	28.7	0.95	27.27	2.08
iodobenzene average yield 2.08 ± 0.04 millimole $99 \pm 1.9\%$						
4.	66	benzene	28.9	0.24	6.94	0.657
	404	bromobenzene	16.2	0.70	11.34	1.0732
5.	67	benzene	24.2	0.22	5.37	0.606
	405	bromobenzene	12.7	0.75	9.53	1.0732
benzene average yield 0.632 ± 0.026 millimole $30 \pm 1.5\%$						

Analyses were performed with bromobenzene as an internal standard. All results were obtained on a Ucon oil LB-550X column with a Perkin Elmer 154 Vapor Fractometer.

The following table shows the results of the experiments conducted on the 10th of May 1900. The results are given in the form of a table, the columns of which are headed as follows:—

Experiment No. 1					
Time	Temp.	Pressure	Volume	Weight	Remarks
10.00	20.0	760.0	100.0	1.000	
10.10	20.0	760.0	100.0	1.000	
10.20	20.0	760.0	100.0	1.000	
10.30	20.0	760.0	100.0	1.000	
10.40	20.0	760.0	100.0	1.000	
10.50	20.0	760.0	100.0	1.000	
11.00	20.0	760.0	100.0	1.000	
11.10	20.0	760.0	100.0	1.000	
11.20	20.0	760.0	100.0	1.000	
11.30	20.0	760.0	100.0	1.000	
11.40	20.0	760.0	100.0	1.000	
11.50	20.0	760.0	100.0	1.000	
12.00	20.0	760.0	100.0	1.000	
12.10	20.0	760.0	100.0	1.000	
12.20	20.0	760.0	100.0	1.000	
12.30	20.0	760.0	100.0	1.000	
12.40	20.0	760.0	100.0	1.000	
12.50	20.0	760.0	100.0	1.000	
13.00	20.0	760.0	100.0	1.000	
13.10	20.0	760.0	100.0	1.000	
13.20	20.0	760.0	100.0	1.000	
13.30	20.0	760.0	100.0	1.000	
13.40	20.0	760.0	100.0	1.000	
13.50	20.0	760.0	100.0	1.000	
14.00	20.0	760.0	100.0	1.000	
14.10	20.0	760.0	100.0	1.000	
14.20	20.0	760.0	100.0	1.000	
14.30	20.0	760.0	100.0	1.000	
14.40	20.0	760.0	100.0	1.000	
14.50	20.0	760.0	100.0	1.000	
15.00	20.0	760.0	100.0	1.000	
15.10	20.0	760.0	100.0	1.000	
15.20	20.0	760.0	100.0	1.000	
15.30	20.0	760.0	100.0	1.000	
15.40	20.0	760.0	100.0	1.000	
15.50	20.0	760.0	100.0	1.000	
16.00	20.0	760.0	100.0	1.000	
16.10	20.0	760.0	100.0	1.000	
16.20	20.0	760.0	100.0	1.000	
16.30	20.0	760.0	100.0	1.000	
16.40	20.0	760.0	100.0	1.000	
16.50	20.0	760.0	100.0	1.000	
17.00	20.0	760.0	100.0	1.000	
17.10	20.0	760.0	100.0	1.000	
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17.30	20.0	760.0	100.0	1.000	
17.40	20.0	760.0	100.0	1.000	
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18.00	20.0	760.0	100.0	1.000	
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19.10	20.0	760.0	100.0	1.000	
19.20	20.0	760.0	100.0	1.000	
19.30	20.0	760.0	100.0	1.000	
19.40	20.0	760.0	100.0	1.000	
19.50	20.0	760.0	100.0	1.000	
20.00	20.0	760.0	100.0	1.000	

The results of the experiments conducted on the 10th of May 1900 are given in the form of a table, the columns of which are headed as follows:—

Time, Temp., Pressure, Volume, Weight, Remarks.

The results of the experiments conducted on the 10th of May 1900 are given in the form of a table, the columns of which are headed as follows:—

Time, Temp., Pressure, Volume, Weight, Remarks.

The almost colorless filtrate was kept overnight at -15° . At first a yellow oil separated which later partly solidified to yield 0.327 g. of dry solid, m.p. $28-44^{\circ}$. The solid was filtered and the filtrate was saved to recover cyclohexyl-2-naphthyl

The solid (m.p. $28-44^{\circ}$) was recrystallized from methanol (10 ml.) to give 0.30 g. of phenyl-2-naphthyl sulfide m.p. $46.5-49.5^{\circ}$, (lit. (30), 51.8°). The crude phenyl-2-naphthyl sulfide (0.30 g.) was oxidized by hydrogen peroxide (0.20 g.) in glacial acetic acid (10 ml.). The mixture was warmed until a clear solution resulted, and then heated for an additional 20 minutes. Enough water was added to produce turbidity (4 ml.). The mixture was warmed until a clear solution again resulted and allowed to slowly cool. The crystals which were collected melted at $111-113^{\circ}$. They were recrystallized from a mixture of ethanol (20 ml.) and water (10 ml.). The pure phenyl-2-naphthyl sulfone melted at 115.5° (lit (30), $115-116^{\circ}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{SO}_2$: S, 11.95; C, 71.61; H, 4.51. Found: S, 11.95; C, 71.34; H, 4.70.

The filtrate from the enriched phenyl-2-naphthyl sulfide (0.327 g.) was cooled to -77° and then rapidly filtered which gave a semisolid, m.p. $25-31^{\circ}$. The infrared spectrum indicated that this material was mostly cyclohexyl-2-naphthyl sulfide. It was recrystallized from a methanol-acetone mixture at low temperature to yield

0.099 g. of material, m.p. $35-45^{\circ}$. The solid (m.p. $35-45^{\circ}$) was dissolved in a mixture of hydrogen peroxide (1 ml.) and glacial acetic acid (14 ml.). The solution was heated on the steam bath for 40 minutes. Water (5 ml.) was added, and the warm solution was allowed to cool slowly. Fine white flakes separated. After recrystallization from a mixture of water and ethanol, the solid melted at $97-99^{\circ}$. Both infrared and nuclear magnetic resonance spectra showed that the solid was fairly pure cyclohexyl-2-naphthyl sulfone.

Anal. Calcd. for C₁₆H₁₈S: C, 79.28; H, 7.49; S, 13.23. Found: C, 79.46; H, 7.61; S, 13.28.

In a subsequent run the distillate from vacuum distillation was analyzed by use of nuclear magnetic resonance and infrared spectra, and it was found to be mostly cyclohexyl-2-naphthyl sulfide, but some phenyl-2-naphthyl sulfide was also present. By the above procedure and recrystallization from methanol pure cyclohexyl-2-naphthyl sulfide was obtained, m.p. $46-47.5^{\circ}$. The combined yield of these two products exceeds 32%.

Irradiation of Diphenyliodonium-2-naphthalenethiolate in Carbon Tetrachloride.

Diphenyliodonium-2-naphthalenethiolate (0.951 g.) was added to a standard-taper round-bottomed flask (50 ml), and chloride ion free carbon tetrachloride (10 ml.) was added. The air was removed by dry nitrogen, and the flask was stoppered. The mixture was vigorously shaken in ultra-

violet light for 42 hours. Bromobenzene (0.274 g.), an internal reference, was added, and gas-liquid chromatography was carried out. Iodobenzene (94%) and chlorobenzene (28%) were found to be present (Table IV).

To diphenyliodonium-2-naphthalenethiolate (5.852 g.) in a standard-taper flask was added carbon tetrachloride (50 ml.), and the air was expelled by means of dry nitrogen. The reaction was complete after four days of vigorous shaking in the presence of ultraviolet light. The contents were filtered, and the precipitate was thoroughly washed with carbon tetrachloride. The precipitate was pure diphenyliodonium chloride (0.242 g.). The yield was 5.8%. The solid was converted to diphenyliodonium iodide.

Anal. Calcd. for $C_{12}H_{10}I_2$: I, 31.1. Found: I, 30.1.

Irradiation of Diphenyliodonium-2-naphthalenethiolate in Tetrahydrofuran.

Diphenyliodonium-2-naphthalenethiolate (1.574 g.) was decomposed by the previous procedure in peroxide free tetrahydrofuran (12 ml.). The exposure time was six hours, and the sample was analysed by gas-liquid chromatography in the usual manner. A 3 microliter sample was analysed on a Ucon oil LB-550-X column. Benzene ($67 \pm 6\%$) and iodobenzene ($100 \pm 7\%$) were found.

Evaporation of the remaining reaction mixture under very low pressure for 3 days, followed by repeated washings of the residue with small quantities of cold

TABLE IV

Quantitative Gas-liquid Chromatography

Analyses for Volatile Products in the Decomposition of
Diphenyliodonium-2-naphthalenethiolate in Carbon Tetrachloride.

Sample No.	Retention time (sec.)	Substance	Peak height	Half width	Area	Yield (millimoles)
5.	297 \pm 1	chlorobenzene	10.9	0.53	5.78	0.606
	512 \pm 2	bromobenzene	20.8	0.80	16.65	1.745
	999 \pm 3	iodobenzene	12.8	1.50	19.2	2.01
6.	-	chlorobenzene	10.6	0.50	5.55	0.600
	-	bromobenzene	20.2	0.80	16.15	1.745
	-	iodobenzene	12.6	1.50	18.9	2.04
7.	-	chlorobenzene	11.2	0.53	5.94	0.608
	-	bromobenzene	21.3	0.80	17.05	1.745
	-	iodobenzene	13.3	1.50	19.95	2.04
iodobenzene average yield					94 \pm 0.9%	
chlorobenzene average yield					28 \pm 0.2%	

Analyses were performed with bromobenzene as an internal standard. All results were obtained on a diisodecylphthalate column with a Perkin Elmer 154 Vapor Fractionator.

methanol, afforded 2,2'-dinaphthyl disulfide. The methanol was evaporated and the residue fractionally distilled. The fraction (b.p. 154-159° /14 mm.) appeared to be the 2-tetrahydrofuran derivative of 2-naphthalenethiolate (XXXI). The sample was too impure for conclusive identification by its nuclear magnetic resonance spectrum, however both NMR and IR spectra indicated that this solid was compound (XXXI). Attempts to further purify and make derivatives of this material failed.

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{S}$: S, 13.95. Found:
S, 13.13.

3. Attempted Decomposition of Diphenyliodonium-p-toluenesulfonate.

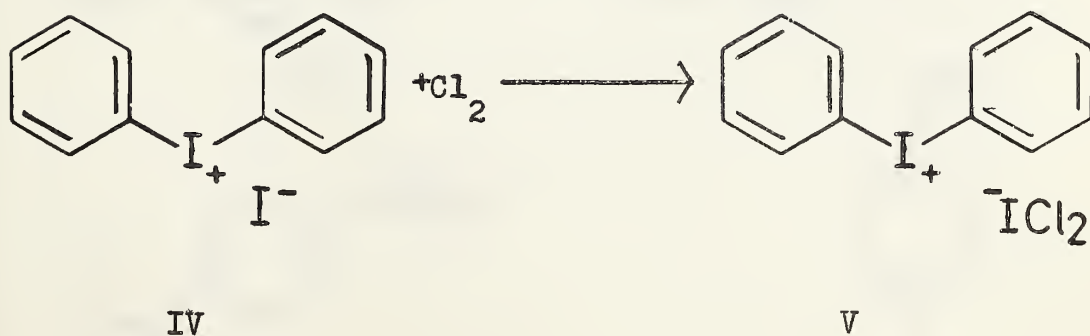
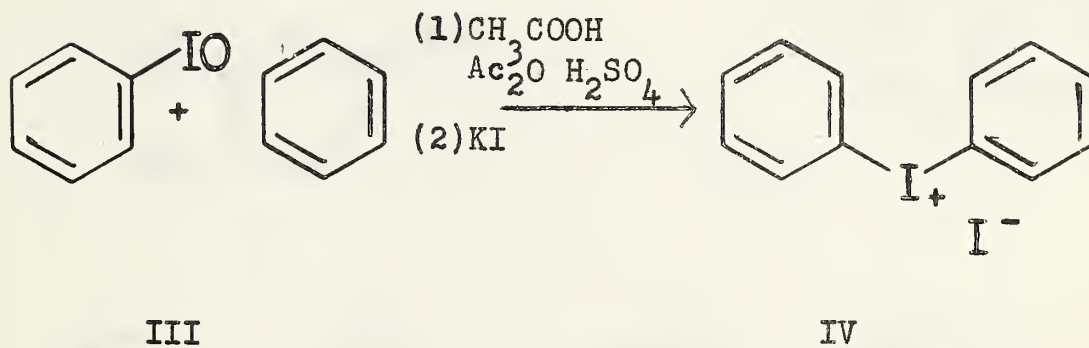
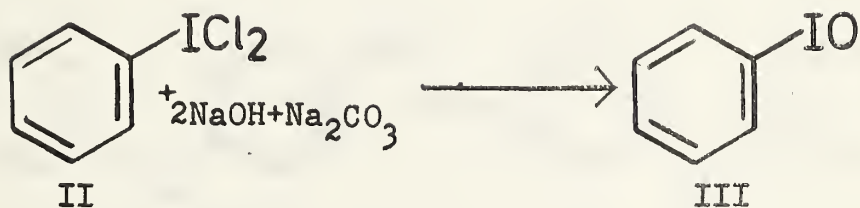
A small amount of diphenyliodonium-p-toluenesulfonate was dissolved in water and a few drops of 10% silver nitrate added. A negative test for chloride ion resulted. Carbon tetrachloride (Mallinckrodt, low sulfur analytical reagent) was shaken with 10% AgNO_3 . This lot of CCl_4 gave a negative chloride ion test and was used in this and subsequent runs.

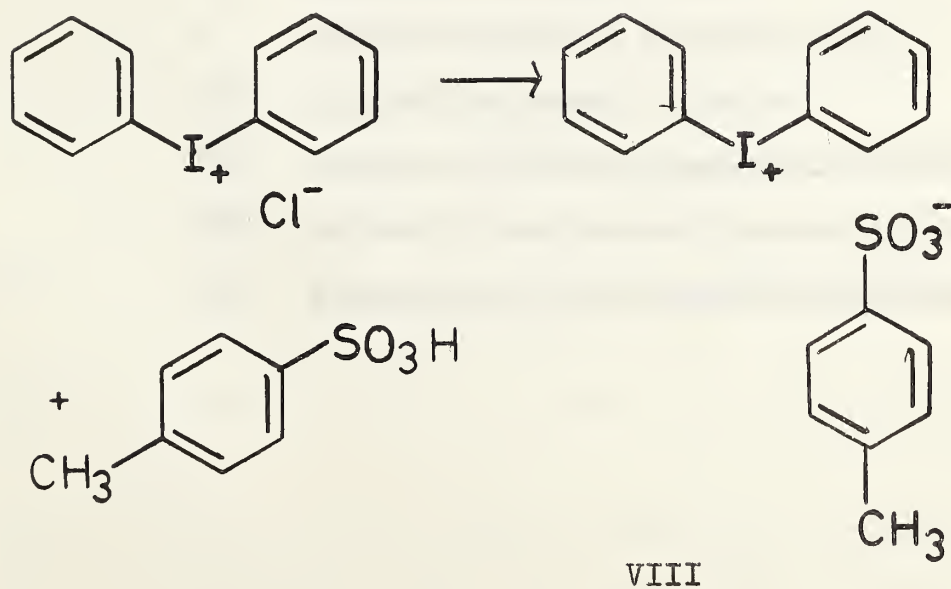
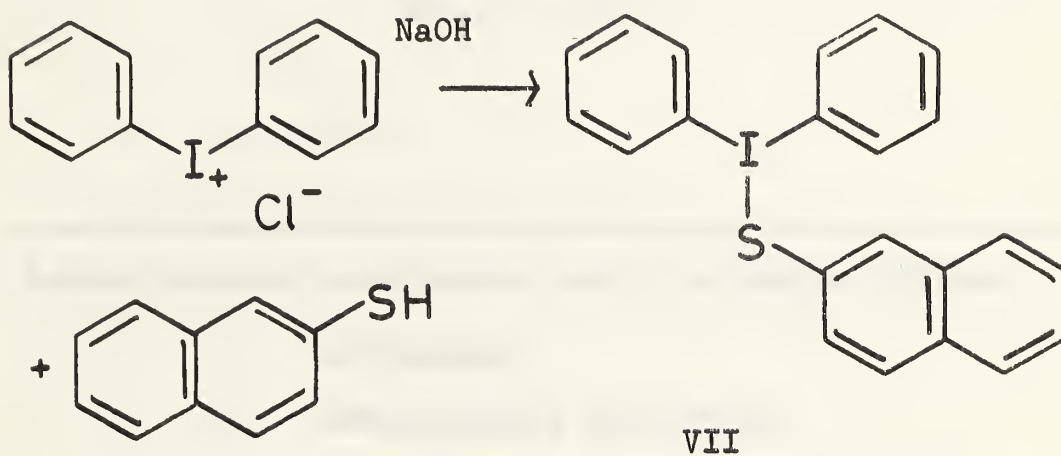
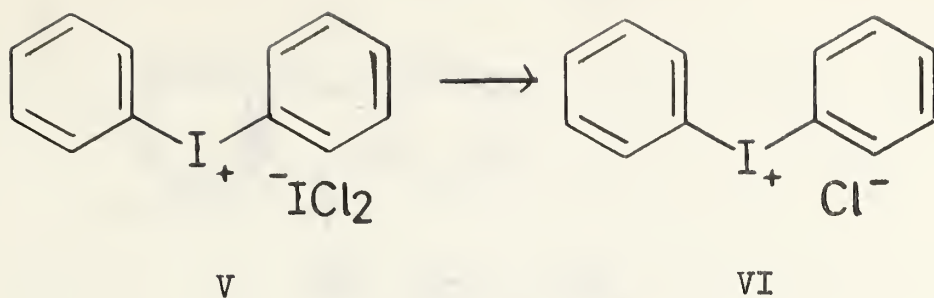
Diphenyliodonium tosylate (0.7717 g.) was added to carbon tetrachloride (10 ml.) in a standard taper flask, and the air removed from the flask by a stream of dry nitrogen. The flask was stoppered and placed in a wrist-action shaker in a beam of ultraviolet light for 4 days. The contents were filtered, and both the solid and filtrate

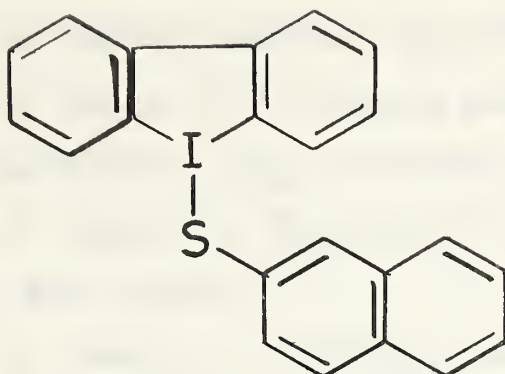
gave negative chloride ion tests. The solid weighed 0.7715 g..

Carbon, hydrogen and sulfur analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Duplicate sulfur and iodine analyses were carried out in this laboratory. All NMR spectra were obtained in CCl_4 on a Varian A60 Spectrometer. Most of the infrared analysis were carried out in dilute solution. Carbon tetrachloride was used whenever possible. Nujol mulls and liquid films were also employed, and all IR spectra were procured on Perkin Elmer 21 & 221 Spectrophotometers. Ultraviolet spectra were obtained in 95% ethanol, and visible spectra were obtained in 95% ethanol, acetonitrile and dimethyl sulfoxide. Preliminary ultraviolet studies were performed with a Cary Model 14M Spectrophotometer, but all data in this thesis was obtained with a Beckman DK-2 ultraviolet/near infrared recording spectrophotometer. All melting points were obtained with a Gallenkamp Melting Point Apparatus and are uncorrected. An appendix listing some important structures follows.

APPENDIX







IX

Nomenclature of structures used in appendix follows:

- I iodobenzene
- II iodosobenzene dichloride
- III iodosobenzene
- IV diphenyliodonium iodide
- V diphenyliodonium dichloroiodate
- VI diphenyliodonium chloride
- VII diphenyliodonium-2-naphthalenethiolate
- VIII diphenyliodonium-p-toluenesulfonate
- IX dibenziolium-2-naphthalenethiolate

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PART II

ABSTRACT

Alkanesulfonic acid esters have frequently proven to be anticancer agents. The "success" of these agents has been attributed to their alkylating ability. Bifunctional alkanesulfonic acid esters were known to be better biological agents. The addition of adjacent carboxyl groups would greatly increase the alkylating property, and for this reason we attempted to prepare a series of α, α' -dimethanesulfonate esters of dihydroxycarboxylic acids and their ethyl esters.

There are practical and excellent theoretical reasons why the isolation and purification of such compounds is difficult and in some cases improbable. One of the difficulties is lactone formation, which can be assisted by neighboring-group participation.

The synthesis and reaction path in the preparation of bi- δ -lactone are discussed, and the lactone itself is interesting from the standpoint of its conformation and infrared spectrum. Optically active α, α' -dibromoadipic acids were prepared and employed in the preparation of bi- δ -lactone.

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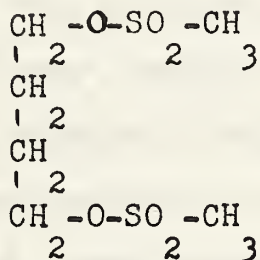
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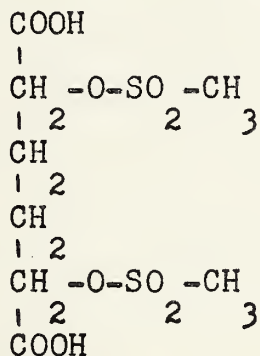
INTRODUCTION

The object of this work was to prepare a 1,4-dicarboxy Myleran. Myleran is the diester of methanesulfonic acid and 1,4-dihydroxybutane. It has the structure,



methanesulfonic acid, tetramethylene ester
(Myleran)
(Busulfan)

and our objective was to prepare the α, α' -dimethanesulfonate ester of dihydroxyadipic acid.



α, α' -dimethanesulfonate ester of dihydroxyadipic acid

Myleran is of considerable importance in cancer chemotherapy especially in the treatment of chronic myelocytic leukemia (1). Myleran is a good alkylating agent. Some

workers believe that it is as effective as the nitrogen mustards in the treatment of cancer, because of this alkylating property. It also seems necessary that the alkylating agent should be a bifunctional one.

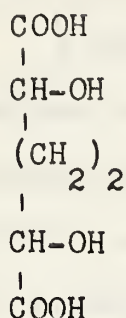
We felt the introduction of two carboxyl groups adjacent to the sulfonate ester functions would increase the alkylating power, because of the well known neighboring-group participation of the adjacent carboxylate ion (2). Although the isolation of the dicarboxylated Myleran was not achieved, some interesting reactions of the starting material, α, α' -dibromoadipic acid, were found.

LITERATURE SURVEY

In 1920 Ingold (3) began a study of the failure of Baeyer's strain theory to account satisfactorily for the relative ease of formation and the stability of the different types of carbon rings. A number of monobasic α -bromo acids were studied in reactions with base. The progress of ring formation in competition with side reaction was considered to be a measure of the ease of production of the ring. At that time very little work was done on the application of the method to the more simply constituted dibasic acids, the α, α' -dihalogen derivatives of which might be expected to yield unsaturated as well as cyclic elimination products.

The extension of the research (4) to α, α' -dibromoadipic acid appeared to afford a valuable opportunity for investigating the products which differ in their stereochemistry. The action of bromine on adipic acid had already been investigated by a number of workers (5, 6, 7). When two molecular proportions of bromine react with the acid chloride of adipic acid, the two dibromoadipic acids formed, differ greatly in melting point and particularly in their solubility in water. The less fusible acid, m.p. 193° , is almost insoluble in cold water, whereas the isomeride, m.p. 139° , dissolves readily.

Rosenlew (6) converted the two isomerides into the corresponding dihydroxyadipic acids,



α, α' -dihydroxyadipic acid

by boiling with water and barium hydroxide. He isolated two acids, m.p. 173° and 134° . The latter acid was much more soluble in water. Rosenlew concluded from their melting points and relative solubilities that the isomeride of m.p. 173° was the racemic and that of m.p. 134° was the meso acid, but he presented no evidence to support this view. LeSueur (7) subsequently prepared the dihydroxyadipic acids from the nearly pure dibromo acid by boiling with water and sodium hydroxide and showed that the two acids, m.p. 174° and 146° were produced. These obviously corresponded to the acids m.p. 173° and 134° obtained by Rosenlew.

In order to decide which of these two α, α' -dihydroxyadipic acids was racemic, LeSueur (7) treated the acid, m.p. 146° , with cinchonidine and obtained a crystalline salt which, on decomposition with ammonia, yielded a d-dihydroxyadipic acid ($[\alpha]_D + 3.8^\circ$). He

concluded that the acid, m.p. 146^o, contrary to the view of Rosenlew, was the racemic acid.

Although there could be little doubt that the view of LeSueur was the correct one, it was clear that the determination of the nature of dihydroxyadipic acids did not afford valid evidence for the configuration of the dibromo acids from which they are derived. Perkin and Robinson (8) examined the products from the reaction of dibromoadipic acid and the sodium derivative of malonic ester. They examined the possible configurations of the acids produced and concluded that the dibromoadipic acid, m.p. 193^o, must be the racemic modification, and that this acid must correspond to the dihydroxyadipic acid, m.p. 146^o, since it is this acid which is resolvable. The meso dihydroxyadipic acid, m.p. 174^o, corresponded therefore to the meso dibromoadipic acid m.p. 139^o.

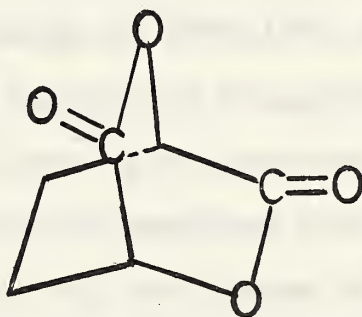
As a result of an interesting series of reactions of the acid of m.p. 193^o Ingold (4) drew a conclusion contrary to that reached by Perkin and Robinson and considered that this acid was the meso variety. An attempt (8) to resolve the dibromoadipic acid of m.p. 193^o by means of morphine was unsuccessful because of the ease with which the acid loses hydrogen bromide on treatment with morphine even in the cold.

Holmberg and Muller (9) in order to settle this controversy regarding which was the meso and which was the dl form, attempted to resolve both inactive α,α' -dibromoadipic

acids, 193° and 139° . They showed that only the lower melting acid could be resolved into optically active components, by progressive formation of the salt with α -(-)-phenylethylamine, followed by recrystallization and recovery of the acid with HCl. The pure optical isomers of α, α' -dibromoadipic acid were found to possess the following rotations:

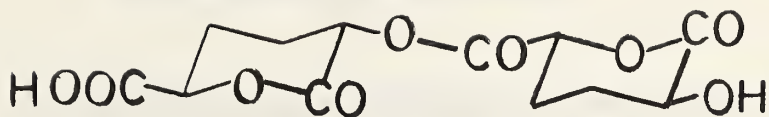
$$\begin{array}{l} \text{d-acid} \quad [\alpha]_D^{18^{\circ}} + 66.3^{\circ}, \text{ m.p. } 151-153^{\circ} \\ \text{l-acid} \quad [\alpha]_D^{18^{\circ}} - 65.1^{\circ}, \text{ m.p. } 151-153^{\circ} \end{array}$$

Since α, α' -dihydroxyadipic acid contains two asymmetric carbon atoms, the existence of a racemic and meso variety was to be expected. LeSueur (7) heated the dihydroxy acid, m.p. 146° , and found that it lost water to give the beautifully crystalline sublimate of its dilactone.



dilactone of α, α' -dihydroxyadipic acid

The other dihydroxyadipic acid, m.p. 174° , when heated lost water, but no trace of a sublimate was formed, and the product consisted of the lactone-lactide of the acid.



lactone-lactide of α, α' -dihydroxyadipic acid

LeSueur explained this formation of different products on the basis of configuration of the isomers. The conformation of this bilactone is very interesting and will be discussed later.

Marvel (10) prepared the dilactone by the method of LeSueur and examined the infrared carbonyl absorption frequency. The carbonyl band is at 1784 cm^{-1} in Nujol mull and 1788 cm^{-1} in chloroform. These frequencies are of interest in that infrared spectrophotometry has been used to distinguish between γ - and δ -lactone ring systems in natural products. A range of $1780\text{-}1760 \text{ cm}^{-1}$ is commonly reported for the $\text{C}=\text{O}$ stretching frequency in saturated γ -lactones and $1750\text{-}1735 \text{ cm}^{-1}$ for saturated δ -lactones (11). Jones and Gallagher (12) examined four kinds of saturated steroid δ -lactones. All four types of δ -lactones exhibit the typical $\text{C}=\text{O}$ stretching band between 1747 and 1737 cm^{-1} in carbon disulfide and carbon tetrachloride solution.

RESULTS AND DISCUSSIONS

1. Syntheses of α -Methanesulfonate Esters of Hydroxycarboxylic Acids and Esters.

In 1960 the chemistry section of Cancer Chemotherapy National Service Center published a report (17) on alkanesulfonic acid esters. In this report it was stated: "We hope that this report will stimulate investigators to synthesize other alkanesulfonic acid esters, because compounds of this class have frequently proven to be active anticancer agents."

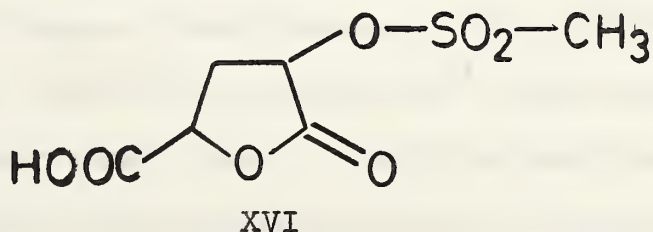
We felt that the introduction of an adjacent carboxyl group would greatly increase the alkylating properties of the methanesulfonic acid ester. When this work was undertaken, only a single compound (17), the methanesulfonate ester of glycolic acid, had been prepared and was undergoing screening for anticarcinogenic activity. From the outset it was realized that the preparation and purification of α -methanesulfonate esters of hydroxy acids might be extremely difficult, if at all possible. However, once prepared the α -methanesulfonate esters of hydroxy acids, might be important potential anticarcinogenic agents because they should be excellent alkylating reagents.

When α -bromopropionic acid was treated with silver methanesulfonate in acetonitrile, the α -methanesulfonate ester of hydroxypropionic acid (XV) was formed in

good yield. The purification of (XV) was very tedious. After repeated recrystallizations from ether-benzene it melted at 50-52°.

We felt that a bifunctional molecule might be a better biological agent. For that reason α,α' -dibromosebacic acid was prepared, and it was treated with silver methanesulfonate in acetonitrile. Only a trace of the α,α' -dimethanesulfonate ester of dihydroxysebacic acid (XVIII) could be isolated. It was a strong acid (pH 1), and it was difficult to purify by recrystallization. Although the structure was confirmed by analysis and infrared spectrum, XVIII could not be isolated in pure form.

When α,α' -dibromoglutaric acid was treated with silver methanesulfonate in acetonitrile under similar conditions, no corresponding dimethanesulfonate ester was obtained. Only a pale-yellow oil remained. This syrup could not be crystallized, and it decomposed on heating. The infrared spectrum supported the structure of a 5-membered substituted lactone.



The lactone carbonyl stretching frequency was at 1790 cm⁻¹ (lit. (11), 1780-1760 cm⁻¹), and the carboxylic

acid carbonyl stretching frequency was at 1740 cm^{-1} . Esters of alkyl sulfonic acids are reported (11) to absorb near 1350 cm^{-1} and 1176 cm^{-1} . We found intense bands at 1355 cm^{-1} and 1180 cm^{-1} . In addition we found that the methyl hydrogen of Myleran had a weak band near 3030 cm^{-1} , and our compound also showed a band at 3030 cm^{-1} to be present. We feel that the anticipated disulfonate ester was not formed because: (1) The methanesulfonate ester is an excellent leaving group. (2) There is neighboring-group participation by an adjacent carboxyl group. (3) There is an overwhelming tendency to form a 5-membered ring.

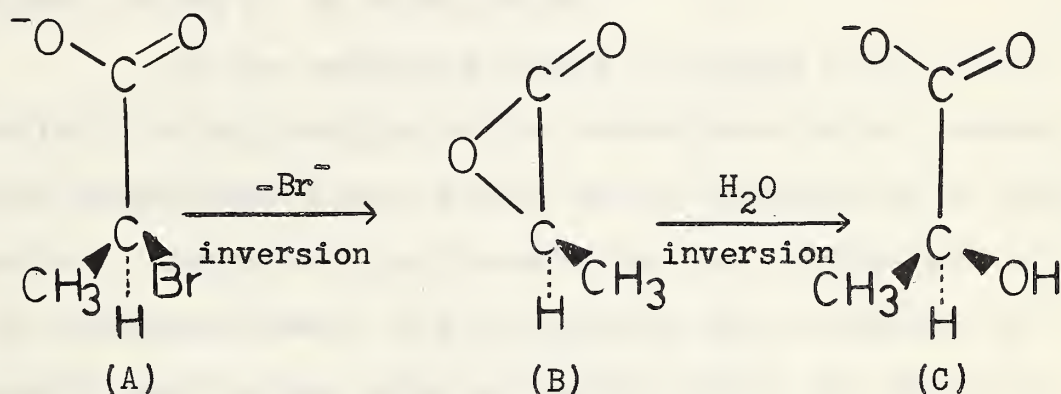
In an identical manner α,α' -dibromoadipic acid was treated with silver methanesulfonate in acetonitrile. There was some evidence that the resulting oil was the α,α' -dimethanesulfonate ester of dihydroxyadipic acid. However the syrupy material underwent reaction with water and alcohol and could not be crystallized. It decomposed on heating. The infrared spectrum had only three intense peaks. A single carbonyl peak was present at 1740 cm^{-1} . The other intense absorptions at 1355 cm^{-1} and 1185 cm^{-1} (lit. (11), 1350 cm^{-1} and 1176 cm^{-1}) were attributed to the sulfonate ester group. Also the small peak at 3030 cm^{-1} was ascribed to the methyl hydrogen of the methanesulfonate ester group. The typical broad OH (hydrogen bonded) stretching vibration for a carboxylic acid was found at $2700\text{-}2500\text{ cm}^{-1}$.

Ethyl α,α' -dibromosebacate and ethyl α,α' -dibromoadipate were treated with silver methanesulfonate in acetonitrile. The resulting α,α' -dimethanesulfonate esters of ethyl dihydroxysebacate (XX) and ethyl dihydroxyadipate (XIX) were formed in good yields. Both XIX and XX were crystalline solids and were purified by recrystallization. 1,4-Dibromobutane was also treated with silver methanesulfonate in acetonitrile. The product, Myleran, was crystalline and was purified by recrystallization from acetone.

2. Factors Influencing the Formation of the α -Methanesulfonate Ester of Hydroxypropionic Acid.

The reactions of α -bromo acids with silver methanesulfonate in acetonitrile are not the same as the corresponding reactions with α -bromo esters and alkyl bromides. Only in the case of α -bromo acids does neighboring-group participation play an important role. The classic example of neighboring-group participation is encountered in the basic hydrolysis of the α -bromopropionate ion (18). Alkaline hydrolysis (OH^-) of the α -bromopropionate ion follows the $\text{S}_{\text{N}}2$ course of inversion. However hydrolysis and alcoholysis of A under nonalkaline conditions apparently proceed by the $\text{S}_{\text{N}}1$ mechanism with practically complete retention of configuration. Hughes and Ingold (19) postulated that the carboxylate substituent forms a weak electrostatic bond with the carbon atom undergoing substitution and thus

maintains the original configuration in the transition state. Winstein (2) made the alternative suggestion that the transition state results from backside attack by the carboxylate group with inversion and simultaneous loss of bromide ion to form the α -lactone (B). The α -lactone ring is rapidly cleaved in the normal fashion with a second inversion which restores the original configuration (C). The overall reaction thus involves two normal S_N2 displacements; the first of which is internal.

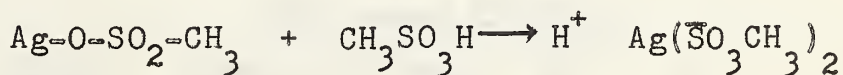


We felt that neighboring-group participation did play an important role in the reaction of α -bromopropionic acid with silver methanesulfonate. If neighboring-group participation occurs in this reaction, then an α -lactone must be an intermediate. Since the carboxylate anion rather than the free carboxylic acid participates, strong acid should suppress the ionization of the free acid and should retard the formation of the α -lactone.

α -Bromopropionic acid was treated with silver

methanesulfonate in acetonitrile and also in water with and without added acid. The extent of reaction was determined by weighing the silver bromide formed in the reaction. There was a large retarding effect by strong acid on the reaction rate in both acetonitrile and water (Tables I & II). Senter (20) treated α -bromopropionic acid and its sodium salt with silver nitrate in water. He reported that the reaction proceeds faster for the sodium salt than for the free acid, and he attributes most of the retarding effect to the H^+ of nitric acid.

If the retarding effect of strong acid is due entirely to suppression of the carboxylate anion, strong acid should have little effect on the reaction of an alkyl halide. Therefore 1,4-dibromobutane was treated with silver methanesulfonate in acetonitrile, and a similar but equally spectacular rate depressing effect was observed (Table III). However the rate retarding effect of strong acid cannot be due entirely to neighboring-group participation. It is quite possible that some type of complex such as



is formed. We were not able to demonstrate the existence of such a complex by spectroscopic means. The presence of such a complex could probably have been established by the use of polarography.

TABLE I

The Reaction of α -Bromopropionic Acid (0.60-0.75 g.) with Silver Methanesulfonate in Acetonitrile (15 ml.) with and without Added Acid.

Run No.	Temp.	Time	Molar Ratio $\text{CH}_3\text{SO}_3\text{Ag}/$ $\text{CH}_3\text{CHBrCOOH}$	Molar Ratio Added Acid/ $\text{CH}_3\text{CHBrCOOH}$	% AgBr
Without added acid					
1a	22-23 ^o	2 days \pm 10 min.	4	-	91.7
b	"	"	4	-	98.4
With added $\text{CH}_3\text{SO}_3\text{H}$					
2a	22-24 ^o	2 days \pm 10 min.	4	1	42.3
b	"	"	4	1	35.2
c	22-23 ^o	"	4	2	18.4
d	"	"	4	2	18.5
e	22-24 ^o	"	4	4	6.7
f	"	"	4	4	5.8
With added CF_3COOH					
3a	22-23 ^o	2 days \pm 10 min.	4	1	66.3
b	"	"	4	1	62.8
c	"	"	4	2	40.7
d	"	"	4	2	42.7
e	22-24 ^o	"	4	4	18.1
f	"	"	4	4	18.9
g	"	"	4	8	2.4
h	"	"	4	8	2.3
With added CH_3COOH					
4a	22-24 ^o	2 days \pm 10 min.	4	1	92.0
b	"	"	4	1	91.4
c	"	"	4	2	78.4
d	"	"	4	2	77.2
e	"	"	4	4	57.4
f	"	"	4	4	57.8
g	"	"	4	8	26.3
h	"	"	4	8	25.5

TABLE II

The Reaction of α -Bromopropionic Acid (0.70-0.75 g.) with Silver Methanesulfonate in Water (15 ml.) with and without Added Acid.

Run No.	Temp.	Time	Molar Ratio $\text{CH}_3\text{SO}_3\text{Ag}/$ $\text{CH}_3\text{CHBrCOOH}$	Molar Ratio Added Acid/ $\text{CH}_3\text{CHBrCOOH}$	% AgBr
Without added acid					
1a	23-24°	360 ± 2 min.	2	-	94.2
b	"	"	2	-	95.5
c	"	240 ± 2 min.	2	-	90.0
d	"	"	2	-	93.5
With added $\text{CH}_3\text{SO}_3\text{H}$					
2a	22-24°	360 ± 2 min.	2	2	63.5
b	"	"	2	2	67.8
c	"	"	2	4	48.0
d	"	"	2	4	47.8
With added CF_3COOH					
3a	22-24°	360 ± 3 min.	2	1	89.9
b	"	"	2	1	89.6
c	"	"	2	2	80.6
d	"	"	2	2	80.9
e	"	"	2	4	71.3
f	"	"	2	4	71.8
With added CH_3COOH					
4a	22-24°	360 ± 3 min.	2	2	95.8
b	"	"	2	2	95.9
c	"	"	2	4	96.0
d	"	"	2	4	96.3
e	"	"	2	8	94.8
f	"	"	2	8	94.2

TABLE III

The Reaction of 1,4'-Dibromobutane (0.70-0.75 g.) with Silver Methanesulfonate in Acetonitrile (15 ml.) with and without Added Acid.

Run No.	Temp.	Time	Molar Ratio $\text{CH}_3\text{SO}_3\text{Ag}/$ $(\text{CH}_2\text{BrCH}_2)_2$	Molar Ratio Added Acid/ $(\text{CH}_2\text{BrCH}_2)_2$	% AgBr
Without added acid					
1a	reflux	4hr.	1.0	-	86.6
b	"	4hr.	1.0	-	91.3
c	"	6hr.	1.1	-	94.3
d	"	6hr.	1.1	-	95.7
With added $\text{CH}_3\text{SO}_3\text{H}$					
2a	reflux	6hr.	1.1	1	41.7
b	"	6hr.	1.1	1	47.6
c	"	6hr.	1.1	2	35.3
d	"	6hr.	1.1	2	43.0
With added CF_3COOH					
3a	reflux	6hr.	1.1	1	65.8
b	"	6hr.	1.1	1	69.4
c	"	6hr.	1.1	2	51.5
d	"	6hr.	1.1	2	45.4
With added CH_3COOH					
4a	reflux	6hr.	1.1	1	87.8
b	"	6hr.	1.1	1	87.5
c	"	6hr.	1.1	2	84.4
d	"	6hr.	1.1	2	80.6

Senter (20) reported that traces of silver bromide may double or triple the rate of substitution with alkyl bromides. This is consistent with the theory that trace amounts of Ag^+ catalyze substitution reactions of alkyl halides (21). In addition stable silver complexes of the type, AgI_2^- are known to accelerate reactions of alkyl halides (22). The mechanism for substitution of bromine in α -bromopropionic acid is therefore complicated by many factors. However, we felt that neighboring-group participation did play an important role.

3. Reaction of α,α' -Dibromoadipic Acids with Weak Bases in Acetonitrile.

When racemic- α,α' -dibromoadipic acid was treated with silver oxide in acetonitrile, an insoluble salt was formed. After refluxing for two days, filtering and evaporating the filtrate, a lactone (bi- δ -lactone) was obtained. LeSueur (7) prepared this lactone by heating racemic- α,α' -dihydroxyadipic acid, m.p. 146° , in a vacuum. He also heated meso- α,α' -dihydroxyadipic acid, m.p. 174° , but in this case LeSueur obtained a lactone-lactide. LeSueur's results were duplicated in this laboratory.

This bi- δ -lactone and its formation provided a challenging study. Marvel (10) prepared this bi- δ -lactone by the method of LeSueur. He cites this lactone as an example of a δ -lactone with a single carbonyl band at high

frequency, 1788 cm^{-1} in chloroform and 1784 cm^{-1} in Nujol. The actual infrared spectrum was not reported. We found an intense carbonyl absorption at 1787 cm^{-1} in chloroform and 1797 cm^{-1} in carbon tetrachloride. The infrared spectrum is reproduced (Fig. 1), and the nuclear magnetic resonance spectrum was obtained in acetonitrile and chloroform. When chloroform was used as the solvent, only two peaks were found (Fig. 2), and the integrated areas under these peaks were in the ratio two:one. The τ -values were 7.73 ($-\text{CH}_2-$) and 5.02 ($-\text{CH}-$).

The same bi- δ -lactone was also prepared from the racemic- α,α' -dibromoadipic acid by use of silver carbonate, sodium carbonate or silver oxide in refluxing acetonitrile. The yields were always $42 \pm 4\%$. Furthermore, when a silver salt was used as the weak base, one-half of the theoretical amount of silver bromide was formed in a few minutes.

The same reaction was carried out using meso- α,α' -dibromoadipic acid. Again regardless of the weak base used, the yields were always the same, viz. $21 \pm 3\%$. Also one of the bromine atoms was immediately replaced. The analyses, infrared spectra and melting points were identical for the bi- δ -lactones derived from the meso and racemic- α,α' -dibromoadipic acids. A mixture of the two lactones had the same melting point as the individual lactones, which melted at $133.5\text{--}134^\circ$.

We became interested in the formation of the bi- δ -

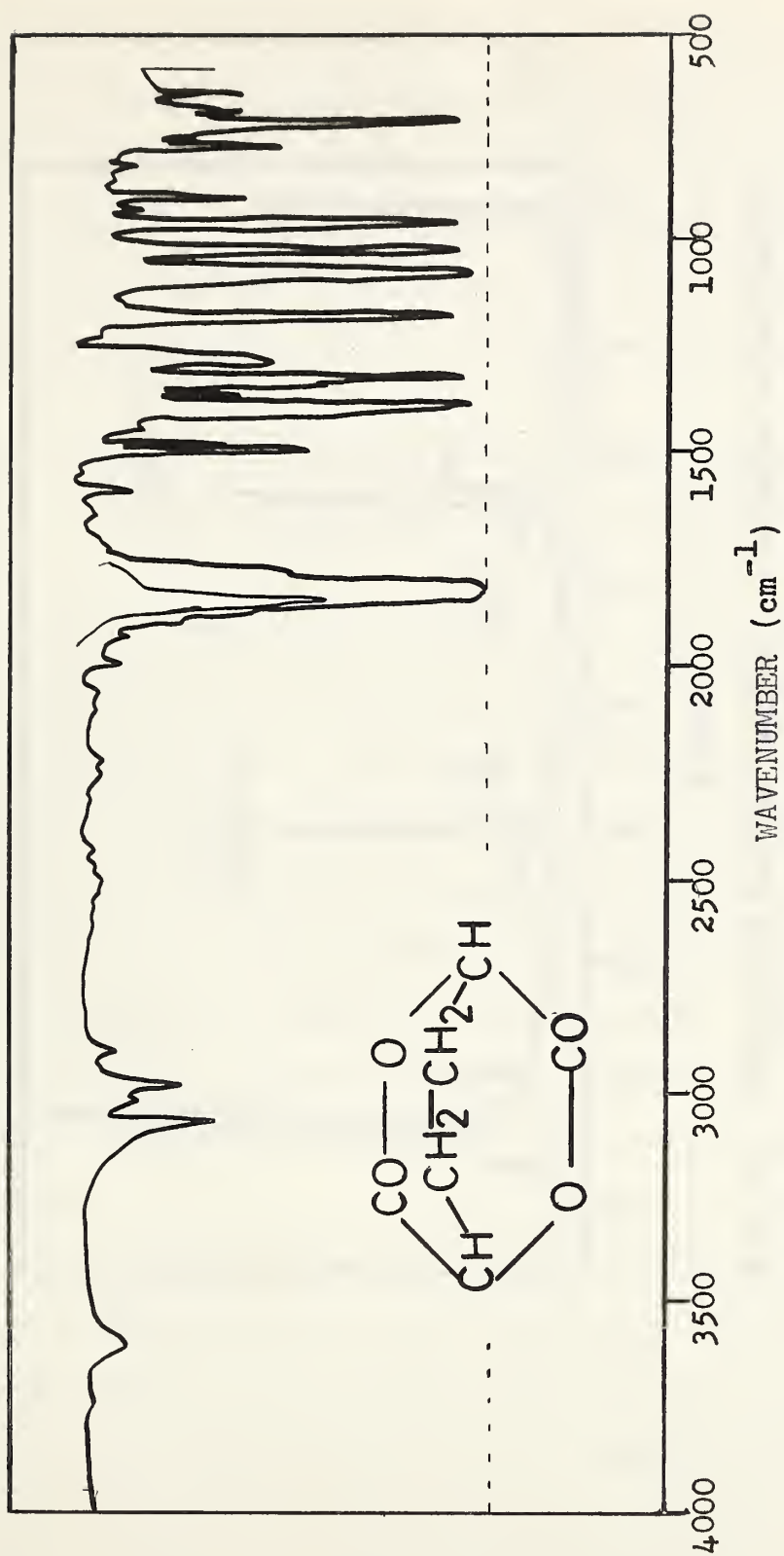


FIG. 1. Infrared spectrum of bi- δ -lactone in chloroform showing the region 4000-600 cm^{-1} . (Perkin Elmer 421)

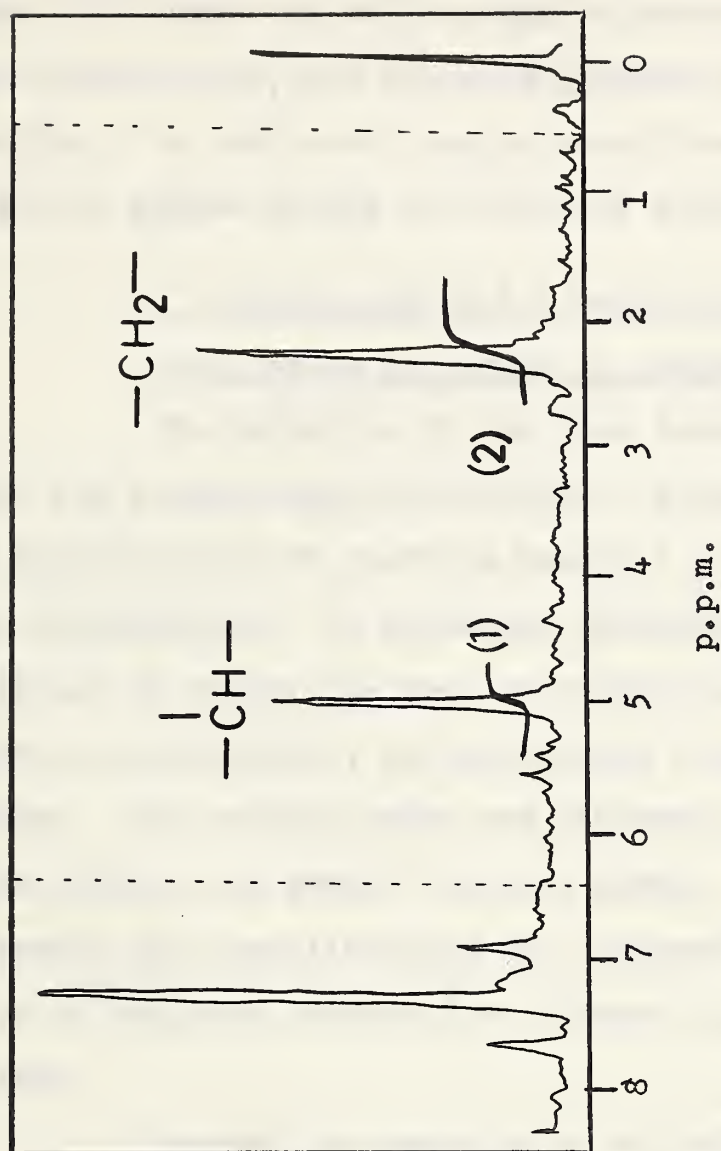


FIG. 2. Integrated nuclear magnetic resonance spectrum of
bi- δ -lactone in chloroform. (Varian A60)

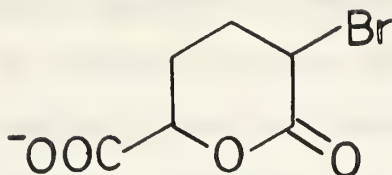
lactone in view of the fact that: (1) The racemic dibromo acid afforded a yield roughly twice that of the meso dibromo acid. (2) Only the racemic- α,α' -dihydroxyadipic acid yielded the bi- δ -lactone, and the meso dihydroxy acid gave a lactone-lactide. We felt much insight about the reaction mechanism might be gained by use of optically active starting materials.

4. Reaction of (d & l)- α,α' -Dibromoadipic Acids with Sodium Carbonate in Acetonitrile.

The formation of the same lactone from both the meso and racemic- α,α' -dibromoadipic acids must be due either to equilibration of starting material or formation of a common intermediate. On prolonged refluxing (2 days) of a solution of either the meso or racemic- α,α' -dibromoadipic acid in acetonitrile, an equilibrium concentration was obtained. The melting point and infrared spectrum indicated this mixture was mostly the meso isomer. At first it appeared that equilibration was responsible for the formation of the same lactone from either the meso or racemic isomer.

However the reaction of α,α' -dibromoadipic acids with sodium carbonate in acetonitrile rapidly forms a double salt, and it is this salt formation that makes the idea of an equilibration of the starting material unattractive. Furthermore, if a silver salt is used as the weak base, one of the bromine atoms is displaced much more rapidly than the second bromine atom. We interpret these results

in favor of the formation of an intermediate monolactone.



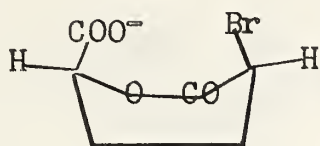
This lactone intermediate was never isolated, but the infrared spectrum supported the structure of an intermediate δ -lactone.

The formation of a monolactone and subsequent bilactone from racemic- α,α' -dibromoadipic acid can be accounted for by two possible reaction paths: (1) Two S_N2 type attacks may occur, the first of which is formation of an α -lactone which is rapidly cleaved by the other carboxylate anion to form the more stable δ -lactone. A single S_N1 attack would give the same δ -lactone. A second S_N1 reaction of the δ -lactone would yield the bilactone. (2) The monolactone might be formed, by a single S_N2 type attack without the assistance of neighboring-group participation. This followed by a second S_N2 attack would afford the bilactone. The possible monolactone conformations are shown in Fig. 3. The meso isomer might also react by an S_N1 and S_N2 or an S_N2 and S_N1 mechanism (Fig. 4).

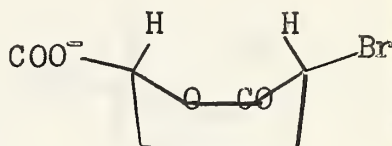
The use of optically active reagents should provide an excellent means of following the reaction mechanism. For that reason racemic- α,α' -dibromoadipic acid was resolved into its enriched isomers by the revised procedure of

Holmberg and Muller (9). Reactions were performed with both the d- and l-isomers. Because the l-isomer was somewhat easier to obtain, its use was preferred. The reaction of the optically active isomers with sodium carbonate in acetonitrile was performed by the same method which was used for the inactive starting material, but on a smaller scale. The yield of bilactone was $37 \pm 3\%$ after a second crystallization from 98% ethanol. The yield of crude product was somewhat higher. The results are tabulated in Table IV.

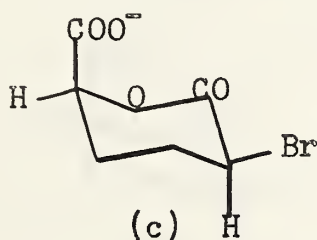
Path (1) two S_N2 or a single S_N1 type attack



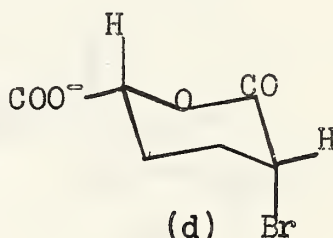
(a)



(b)

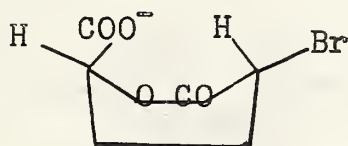


(c)

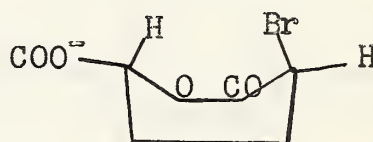


(d)

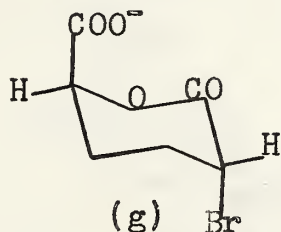
Path (2) a single S_N2 type attack



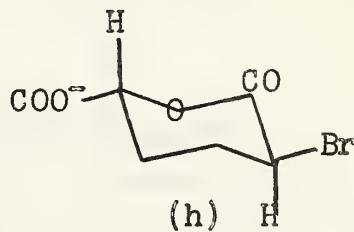
(e)



(f)



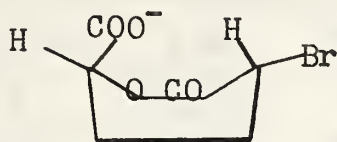
(g)



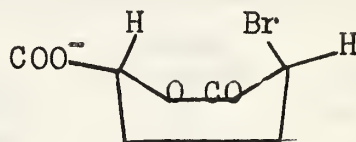
(h)

FIG 3. Possible conformations of the intermediate mono-lactone in the reaction of racemic- α,α' -dibromo-adipic acid with sodium carbonate in acetonitrile.

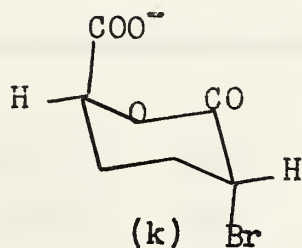
Path (1) two S_N2 or a single S_N1 type attack



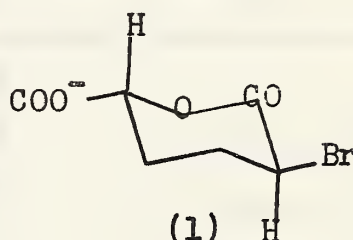
(i)



(j)

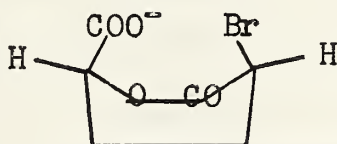


(k)

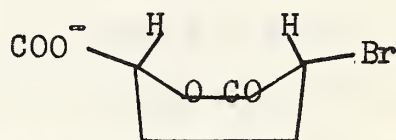


(l)

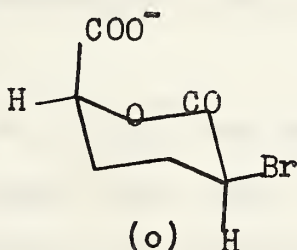
Path (2) a single S_N2 type attack



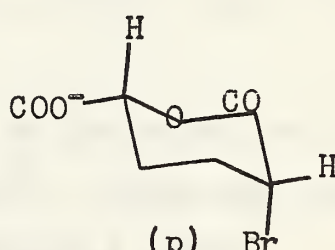
(m)



(n)



(o)



(p)

FIG 4. Possible conformations of the intermediate mono-lactone in the reaction of meso- α,α' -dibromoadipic acid with sodium carbonate in acetonitrile.

TABLE IV

Specific Rotations of (d & l)- α,α' -Dibromoadipic Acids and Resulting Bi- δ -lactones.

Run No.	Rotation of Acid $^{25^\circ}$ $(\alpha)_D$	% of Optically Active Stereo-isomer*	Maximum Possible Rotation of Lactone $^{25^\circ}$ $(\alpha)_D$ **	Actual Rotation of Lactone $^{25^\circ}$ $(\alpha)_D$	% Retained Activity
l-acid					
1	$-19.3 \pm 1^\circ$	64.5	-4.49°	$-1.06 \pm 0.10^\circ$	23.6
2	$-60.0 \pm 1^\circ$	95.0	-13.95°	$-3.38 \pm 0.17^\circ$	24.2
3	$-43.5 \pm 1^\circ$	82.7	-10.17°	$-2.39 \pm 0.24^\circ$	23.5
d-acid					
4	$+15.9 \pm 1$	61.2	$+3.46^\circ$	$+0.885 \pm 0.29^\circ$	25.5
5	"	"	"	$+0.55 \pm 0.40^\circ$	#
6	"	"	"	$+0.85 \pm 0.55^\circ$	#

* -66.3° was assumed to be the rotation of pure l- α,α' -dibromoadipic acid (lit. (9), $(\alpha)_D^{18^\circ} -66.3^\circ$ (5% in ethanol)).

** -15.5° was assumed to be the rotation of pure (-)-bilactone (lit. (15), $(\alpha)_D -15.5^\circ$). These two assumptions were considered to be within experimental error.

The rotations were definitely positive, but the experimental error was very large.

All rotations were obtained with a Rudolph Model 80 Polarimeter (5% in acetone).

Since approximately 25% of the optical activity was retained, most of the 1- α,α' -dibromoadipic acid must have been converted to the monolactone with net retention of configuration. We feel that this intermediate monolactone is most probably formed by a reaction with two S_N2 type displacements. The first displacement is the formation of the strained α -lactone with the assistance of neighboring-group participation. The second is a rapid attack by the second carboxylate anion to form the monolactone (conformations c & d). In the chair conformation (c) the carboxylate anion is in position for an S_N1 type attack on the carbon carrying the bromine atom. Since both the carboxylate anion and the bromine are in the "flagstaff" positions in conformation (a), this conformation must be energetically unfavorable. However, an examination of conformation (a) with Dreiding models shows the carboxylate anion is in an excellent position to displace the bromine atom. The bi- δ -lactone is really a mono- δ -lactone in the boat conformation with the carboxylate group forming a 1,4-bridge. The relatively long refluxing period required can be explained, in part, if the boat conformation is the reactive species.

Originally we felt the difference in yield between the meso ($21 \pm 3\%$) and the racemic ($42 \pm 4\%$) isomers might be due to different reaction rates. However, on refluxing the meso acid with sodium carbonate in acetonitrile for

14 days did not increase the yield. In some runs the optimum yield was obtained in much less time (6 hours). The yields stated are for the bi- δ -lactone crystallized from 98% ethanol. The yield of crude product was somewhat greater, but the crude product was impure. The formation of hydroxy acids, insoluble salts and intermolecular condensation products must influence the yields.

EXPERIMENTAL SECTION

α -Bromopropionic Acid (I).

The α -bromopropionic acid was Eastman white label grade. This colorless liquid, m.p. 22-25^o, was used without further purification.

α,α' -Dibromoadipic Acids (II & III) and Diethyl Esters (IV).

The bromination of adipyl chloride was carried out in a 500 ml. three-necked round-bottomed flask, which was equipped with an efficient condenser, stopper and dropping funnel and mounted on a thermo-stirrer. To freshly distilled Eastman white label adipyl chloride (100 g.), b.p. 84-85^o (3 mm.), was added dry bromine (200 g.). The addition took about 8 hours when heated gently and catalyzed by ultraviolet light.

The α,α' -dibromoadipyl chloride was purged with dry nitrogen to remove the excess bromine. The warm acid chloride was added to distilled water (1350 ml.) at 0^o, and the mixture was vigorously stirred for 8 hours at 0^o to assure complete hydrolysis (9). The precipitate was filtered on a sintered glass funnel, sucked dry and washed three times with cold water (100 ml. each). All the filtrates were combined to recover the dl- α,α' -dibromoadipic acid (II). The dried solid (120 g.) was mostly meso- α,α' -dibromoadipic acid (III), m.p. 170-185^o. The yield of the

enriched meso isomer was 70%. By repeated recrystallization from hot 90% formic acid the pure meso acid was obtained, m.p. 188-193^o (lit. (4), 191-193^o).

The combined filtrates and washings from the hydrolysis were decolorized with a trace of sodium bisulfite, saturated with common salt and extracted with 4 portions of ether (300 ml. each). The ethereal extracts were combined, dried over calcium chloride, filtered and evaporated below 60^o. The resulting viscous yellow oil solidified completely on standing. The solid (55 g.) was crystallized from hot 90% formic acid (150 ml.) to give II (28.5 g.), m.p. 130-135^o. All filtrates from the recrystallizations were saved and reworked. The yield of the crude racemic- α,α' -dibromoadipic acid (II) was about 28%, and the overall yield of II and III combined was always 90-99%.

In a subsequent run a mixture of the ethyl (meso and racemic)- α,α' -dibromoadipate (IV) was prepared by the method of Ingold (4). Warm α,α' -dibromoadipyl chloride (100 ml.) was poured into an excess of absolute ethanol (250 ml.). On cooling most of the liquid solidified, and the resulting solid appeared to be the enriched meso isomer, m.p. 60-65^o (lit. (4), 66^o). The yield of IV was 90%. No attempt to separate IV into the meso and racemic modification was made, since the dl isomer was reported (4) to revert back to the meso form.

α,α' -Dibromoglutaric Acids (VI & VII) and Diethyl Esters (VIII).

Eastman white label glutaric acid (200 g.) was converted to its acid chloride by heating it with Eastman white label thionyl chloride (400 g.) until no more sulfur dioxide was evolved. The bromination of this glutaryl chloride was performed under the same conditions as the bromination of adipyl chloride. Bromine (175 ml.) was slowly added to the glutaryl chloride, and the resulting oil (265 ml.) was divided into two portions for the preparation of the corresponding acids and esters.

To absolute ethanol (150 ml.) was added warm α,α' -dibromoglutaryl chloride (75 ml.). The reaction mixture was heated on the steam bath for 30 minutes to assure complete reaction and to evaporate most of the ethanol. Water (150 ml.) was added, and the mixture was extracted twice with ether (150 ml.). The ether layers were combined and shaken with 4N sodium carbonate (100 ml. each) until the base was only slightly discolored. The ether layer was dried over MgSO_4 , decolorized, filtered and evaporated. This mixture of ethyl (dl & meso)- α,α' -dibromoglutarate esters (VIII) was vacuum distilled using a highly efficient column. The yield of VIII was 88 g. (60%), b.p. 101-103° at 0.5 mm. (lit. (3), b.p. 174-175° (21 mm.)).

To 90% formic acid (500 ml.) was added warm α,α' -dibromoglutaryl chloride (190 ml.), and the mixture

was heated on the steam bath for 30 minutes to ensure complete hydrolysis. The formic acid solution was allowed to cool and stand at 5° for 2 days. After filtering and drying the solid, m.p. 160-165°, weighed 222 g. (71%). The separation of this mixture into its dl and meso isomers has been reported (3), and by this method meso- α,α' -dibromoglutaric acid (VII), m.p. 165-170° was obtained. After three recrystallizations of VII from ether-chloroform 64 g. of solid were obtained, 168-172° (lit. (3), 170°). However, this method was not entirely satisfactory for the isolation of the dl- α,α' -dibromoglutaric acid (VI). Only 20 g. of enriched dl isomer were realized. After three recrystallizations of VI from acetone-benzene 5 g. were obtained, m.p. 135-140° (lit. (3), 142°).

α,α' -Dibromosebacic Acid (X) and Diethyl Ester (XI).

Dry bromine (300 g.) was slowly added to Eastman white label sebacyl chloride (200 g.), and bromination was performed as with the adipyl chloride. The entire addition took about six hours. After removal of excess bromine by purging with dry nitrogen, the warm α,α' -dibromosebacyl chloride (IX) was directly converted to the corresponding acid and ester. Part of IX (175 ml.) was slowly added with stirring to hot 90% formic acid. The α,α' -dibromosebacic acid (X) weighed 212 g., m.p. 114-119°. After two recrystallizations from the minimum quantity of boiling chloroform,

the melting point was raised to 116-120^o (lit.(13), 117-120^o). No attempt has been made to separate this acid into the meso and racemic isomers.

To prepare the ethyl α,α' -dibromosebacate (XI) the remaining portion of IX (75 ml.) was slowly added to hot absolute ethanol (100 ml.). The addition took about 20 minutes, and the solution was heated for an hour on the steam bath to complete esterification and to evaporate the excess ethanol. The residue was distilled, b.p. 203-207^o (2.5 mm.). Some decomposition of XI took place, but the distillate (75 g.) was perfectly clear. The combined yield of the acid (X) and ester (XI) was 95%.

Hydrolyses of (dl & meso)- α,α' -Dibromoadipic Acids (II & III).

Meso- α,α' -dibromoadipic acid (9.12 g.) was added to water (100 ml), and silver oxide (7.66 g.) was added to this mixture. The reaction mixture was refluxed for three days. The silver bromide was filtered, and the filtrate was evaporated under reduced pressure to give a residue (4.5 g.). This was dissolved in the minimum quantity of ethanol, and a few drops of hexane made the solution slightly turbid. The solid that precipitated weighed 2.0 g. (38%), m.p. 140-150^o. By repeated recrystallization from methyl ethyl ketone a small amount of meso- α,α' -dihydroxyadipic acid (XII), m.p. 170-171^o (lit.(4), 174^o), was obtained.

The method of Ingold (4) was employed for the preparation of the dl- α,α' -dihydroxyadipic acid (XIII). Only a trace of (XIII) could be separated in pure form, m.p. 140-145^o from n-propanol (lit.(4), 146^o).

Reaction of 1,4-Dibromobutane with Silver Methanesulfonate.

Silver methanesulfonate (XIV) was prepared by the reaction of Fisher reagent silver oxide with Eastman white label methanesulfonic acid in water. After three recrystallizations from water XIV was obtained in a pure condition. Silver methanesulfonate (35 g.) was dissolved in Fisher reagent acetonitrile (150 ml.), and Eastman white label 1,4-dibromobutane (17.9 g.) was added. The mixture was refluxed for one hour and filtered. The filtrate was refluxed for five hours and filtered. The filtrate was evaporated to a small volume (40 ml.), and ether (200 ml.) was added until turbidity persisted. The mixture was allowed to stand until precipitation was complete. The solid was filtered and washed with ether, and recrystallization of this solid from acetone afforded fine white crystalline Myleran, m.p. 117^o (lit.(16), 114-118^o from ethanol).

Reaction of α -Bromopropionic Acid with Silver Methanesulfonate in Acetonitrile.

Silver methanesulfonate (142 g.) was dissolved

in acetonitrile (500 ml.), and α -bromopropionic acid (53.8 g.) was added. The reaction mixture was heated for two days. The solid, silver bromide, was filtered, and the filtrate was refluxed for four hours and filtered again. The solvent was removed under reduced pressure. The resulting viscous mass was extracted four times with anhydrous ether (200 ml.). After evaporation of the ether the syrup was allowed to stand for one day at -15° after which it solidified. The dried solid weighed 59 g. (88%), m.p. $44-50^{\circ}$. After three recrystallizations from ether-benzene, the methanesulfonate ester of α -hydroxypropionic acid melted at $50-52^{\circ}$.

Anal. Calcd. for $C_4H_6O_4S_2$: S, 19.07. Found: S, 19.06.

Reaction of α,α' -Dibromoglutaric Acid with Silver Methanesulfonate in Acetonitrile.

Meso- α,α' -dibromoglutaric acid (5.0 g.) was dissolved in acetonitrile (75 ml.), and silver methanesulfonate (13.95 g.) was added. The reaction mixture was refluxed for one day, then filtered to remove silver bromide, yield 99%. The filtrate was evaporated at room temperature under vacuum, and the resulting oil was taken up in acetone (10 ml.) and again filtered. The filtrate was evaporated under reduced pressure, and the oily residue was extracted four times with anhydrous ether (200 ml.).

After evaporation of the ether and drying overnight in a vacuum the pale-yellow syrup which was left had a pH 1 when tested with universal indicator paper. Since no precipitate resulted when this oil was dissolved in water and tested with sodium chloride, silver methanesulfonate must have been absent. The infrared spectrum supports the structure of a substituted five-membered lactone (XVI, page 9). Attempts to purify this oil failed. Decomposition occurred on heating, and decomposition also occurred in water and in alcohols.

Reaction of α,α' -Dibromoadipic Acids with Silver Methanesulfonate in Acetonitrile.

Racemic- α,α' -dibromoadipic acid (5.0 g.) was dissolved in acetonitrile (75 ml.), and silver methanesulfonate was added. The reaction mixture was refluxed for one day, and the procedure was identical to that for the preceding dibromoglutaric acid. The infrared spectrum supports the structure of the α,α' -dimethanesulfonate ester of dihydroxyadipic acid (XVII). Compound (XVII) could not be isolated in pure form. The meso- α,α' -dibromoadipic acid behaves in an identical manner with that of the dl isomer in the reaction with silver methanesulfonate in acetonitrile.

Reaction of α,α' -Dibromosebacic Acid with Silver Methanesulfonate in Acetonitrile.

α,α' -Dibromosebacic acid (12.0 g.) was dissolved

in warm acetonitrile (100 ml.), and to this solution was added silver methanesulfonate (27.1 g.). The reaction mixture was refluxed for 15 hours and filtered. The filtrate was evaporated to dryness, and the residue was extracted with acetone. The insoluble material (13.1 g.) was almost pure silver methanesulfonate. The combined acetone extracts were evaporated first on the steam bath then under reduced pressure. The viscous residue was taken up in the minimum quantity of spectro grade methylene chloride, and then enough toluene was added to produce a turbidity. The almost clear solution was stored at -15° for one day. The resulting semisolid was filtered and recrystallized twice from acetone-methylene chloride. The recrystallized α,α' -dimethanesulfonate ester of dihydroxysebacic acid (XVIII) melted over a wide range, $90-125^{\circ}$.

Anal. Calcd. for C H O S : S, 16.41. Found:
12.22 10.2
S, 16.43.

Reaction of Ethyl α,α' -Dibromoadipate with Silver Methanesulfonate in Acetonitrile.

To meso-ethyl α,α' -dibromoadipate (7.2 g.) in acetonitrile (100 ml.) was added silver methanesulfonate (9.0 g.). The reaction mixture was refluxed with stirring for three days and then filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was extracted twice with cold acetone (150 ml.). The

combined acetone extracts were evaporated. The resulting solid was recrystallized twice from ethanol to give the α,α' -dimethanesulfonate ester of ethyl dihydroxyadipate (XIX) in 39% yield, m.p. $92.5-93.5^{\circ}$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_{10}\text{S}_2$: S, 16.43. Found: S, 16.35, 16.34.

Reaction of Ethyl α,α' -Dibromosebacate with Silver Methanesulfonate in Acetonitrile.

To α,α' -dibromosebacate (8.3 g.) in acetonitrile (100 ml.) was added silver methanesulfonate (8.9 g.). The reaction mixture was refluxed for one day with stirring and then filtered. The filtrate was evaporated to dryness in a vacuum, and the residue was extracted twice with cold acetone (200 ml. total). After most of the acetone was evaporated, the residue was dissolved in the minimum volume of ether. By allowing the ether to evaporate slowly crystals formed at the surface of the ether. The solid, m.p. $58-61^{\circ}$, was collected. After two more recrystallizations in this manner the melting point of α,α' -dimethanesulfonate ester of ethyl dihydroxysebacate (XX) remained constant, m.p. $72-74^{\circ}$.

Rate Runs: Reactions of Some α -Bromoacids with Silver Methanesulfonate in Acetonitrile.

All rate runs were performed either at solvent reflux temperature or in a constant temperature bath ($24 \pm 1^{\circ}$).

The actual temperatures are stated for each run. Ace standard-taper round-bottomed flasks (50 ml., 19/38) were employed. All other equipment was standardized, and stirring was carried out at a uniform rate. The solvents used were distilled water and Fisher reagent acetonitrile (15 ml./g. of reagent). At the termination of reaction time the contents were immediately filtered in Pyrex-M sintered glass funnels (30 ml.), and they were heated at 110° for four hours then weighed. A second heating and weighing was carried out as a check. The weight differences were always within 0.5 mg.

Reaction of α,α' -Dibromoadipic Acids with Weak Bases in Acetonitrile.

Meso- α,α' -dibromoadipic acid (200 g.) was added to acetonitrile (1 liter), and anhydrous sodium carbonate (73.5 g.) was added. The mixture was refluxed with stirring for two days and then filtered. The filtrate was evaporated to dryness under reduced pressure and washed with a small volume of ether. The solid was crystallized from the minimum volume of hot 98% ethanol. The yield was 19.1 g. (20.4%), m.p. $133-134^{\circ}$. After two recrystallizations from ethanol it melted at $133.5-134^{\circ}$. In subsequent runs using the same conditions as above with Na CO_2 , Ag CO_2 or Ag O_2 , the yields were always $21 \pm 3\%$.

Racemic- α,α' -dibromoadipic acid (10.0 g.) was dissolved in acetonitrile (100 ml.), and anhydrous sodium

carbonate (3.8 g.) was added. The mixture was refluxed for two days, and the product was isolated by the same procedure used for the product from the meso isomer. The lactone (XXI) crystallized from ethanol weighed 1.88 g. (40.1%), m.p. $133.5-134^{\circ}$. Recrystallization of XXI from ethanol did not change the melting point. Subsequent runs with Na CO_2 , Ag_2O or Ag_2CO_3 under the above conditions always gave yields of $42 \pm 4\%$. The infrared and nuclear magnetic resonance spectra, as well as the melting points of the lactones derived from both the dl and meso isomers, were identical. A mixture of these two lactones also melted at $133.5-134^{\circ}$.

Anal. Calcd. for $\text{C}_6\text{H}_6\text{O}_4$: C, 50.71; H, 4.26.
Found: C, 50.49; H, 4.23.

Meso-dl-dibromoglutaric acid (12.7 g.) was dissolved in acetonitrile (100 ml.), and anhydrous sodium carbonate (4.7 g.) was added. The reaction was carried out and worked up in the same way as the meso-dl-dibromoadipic acid. However, after washing with ether only an insoluble oil remained. This oil turned semisolid at -15° , but it could not be crystallized. On heating, this material decomposed. The infrared spectrum confirmed the presence of a five-membered lactone with a carboxyl group.

Resolution of dl-dl-Dibromoadipic Acid.

After several attempts to resolve racemic-dl-dl-

dibromoadipic acid with brucine had failed, the revised procedure of Holmberg and Muller (9) was employed.

Racemic- α,α' -dibromoadipic acid (8.5 g., m.p. 138-139^o) was added to cold water (100 ml.), and (+)- α -phenylethylamine (3.4 g., (α)_D^{25^o} +40.1^o), prepared by the method of Lovin (14), was added. The mixture was shaken until solution was almost complete. The reaction was exothermic, and almost all of the free acid went into solution before the salt began to precipitate. The partly crystalline material was allowed to stand first at room temperature and then overnight at 5^o. After filtering, the solid was added to 4N hydrochloric acid (20 ml.), and the solution was extracted with three portions of ether (15 ml. each). The ethereal extracts were combined, dried over magnesium sulfate, filtered and evaporated in a rotary evaporator. The last traces of ether were removed under reduced pressure. The yield from the precipitated salt was 2.99 g., (α)_D^{25^o} +4.0^o (5% in acetone). By repeating this procedure several times with the enriched d-isomer, the (+)- α,α' -dibromoadipic acid (1.59 g.) was realized. This enriched d-isomer melted 137-139^o, (α)_D^{25^o} +18.6^o (5% in acetone). Holmberg and Muller (9) reported the m.p. 151-153^o, (α)_D^{18^o} +66.3^o (5% in ethanol).

To the original filtrate was added conc. hydrochloric acid (10 ml.). The extraction and isolation of the α,α' -dibromoadipic acid were performed as above, and the

yield from the filtrate was 3.96 g., $(\alpha)_D^{25^\circ} -3.63^\circ$ (5% in acetone).

To obtain the $(-)\text{-}\alpha,\alpha'$ -dibromoadipic acid the previous procedure was modified. Two equivalents of $(-)\text{-}\alpha$ -phenylethylamine (14) were used. Racemic- α,α' -dibromoadipic acid (5.25 g., m.p. $137\text{--}139^\circ$) was added to water (20 ml.), and this mixture was shaken and cooled to 0° . $(-)\text{-}\alpha$ -Phenylethylamine (4.29 g., $(\alpha)_D^{25^\circ} -40.4^\circ$ (pure liquid)) was added with vigorous stirring and cooling in an ice bath. The temperature was kept below 10° during the addition, and the reaction mixture was stored for one day at 5° . The salt was filtered. The recovery of the free acid from the salt was achieved by the previous procedure. The yield from the filtrate was 3.24 g., $(\alpha)_D^{25^\circ} +4.8^\circ$ (5% in acetone), and the yield from the solid was 1.16 g., $(\alpha)_D^{25^\circ} -19.3^\circ$ (5% in acetone). After several repetitions of this procedure with the enriched l-isomer, $(-)\text{-}\alpha,\alpha'$ -dibromoadipic acid (0.2 g.) was obtained, and melted at $149\text{--}151.5^\circ$, $(\alpha)_D^{25^\circ} -60.1^\circ$ (5% in acetone). Holmberg and Muller reported the m.p. $151\text{--}153^\circ$, $(\alpha)_D^{18^\circ} -65.1^\circ$ (5% in ethanol). Many complete runs were performed.

Reaction of (d & l)- α,α' -Dibromoadipic Acids with Sodium Carbonate in Acetonitrile.

To $(-)\text{-}\alpha,\alpha'$ -dibromoadipic acid (0.75 g., $(\alpha)_D^{25^\circ} -60.1^\circ$ (5% in acetone) dissolved in Fisher reagent acetonitrile (25 ml.) was added a slight excess of sodium car-

bonate (0.287 g.), and the reaction mixture was refluxed for 48 hours. The product was recovered in the same way as the inactive lactone. The optically active lactone after two recrystallizations from 98% ethanol melted 129-131^o, 0.134 g. (38.3%), $(\alpha)_D^{25} -3.38 \pm 0.17^o$ (5% in acetone). Freudenberg and co-workers (15) prepared this optically active lactone ($(\alpha)_D -15.5^o$) from (-)- α,α' -dihydroxyadipic acid.

Anal. Calcd. for C₆H₆O₄ : C, 50.71; H, 4.26.

Found: C, 50.73; H, 4.32.

A series of runs was carried out with the (-)- α,α' -dibromo-adipic acid. When (+)- α,α' -dibromoadipic acid ($(\alpha)_D^{25} +15.9^o$ (5% in acetone)) was used as the starting material, a lactone, m.p. 132-133.5^o, yield 37.8%, was obtained. This lactone had a rotation $(\alpha)_D^{25} +0.885 \pm 0.29^o$ (5% in acetone).

Anal. Calcd. for C₆H₆O₄ : C, 50.71; H, 4.26. Found:

C, 50.67; H, 4.22.

Equilibration of α,α' -Dibromoadipic Acids in Acetonitrile.

Pure meso- α,α' -dibromoadipic acid (2.0 g., m.p. 188-193^o) was dissolved in reagent acetonitrile (25 ml.) and was refluxed for 48 hours and then filtered. The clear filtrate was evaporated to dryness under reduced pressure, and the resulting solid was recrystallized from acetonitrile. This solid will be referred to as A.

Pure racemic- α,α' -dibromoadipic acid (2.0 g., m.p. 137.5-139^o) was dissolved in reagent acetonitrile (25 ml.) and refluxed for 48 hours and then filtered. The evaporation and recrystallization were carried out in the same way as for the meso isomer. This solid will be referred to as B.

The racemic acid was more soluble than the meso acid in acetonitrile. However, A and B had similar solubilities in acetonitrile. They had identical melting points, 181-186^o, and their spectra were superimposable. A mixture of A and B also melted 181-186^o. The spectrum of A or B was different from the infrared spectrum of either the dl- or meso acid, but it was closer to the spectrum of the meso acid.

Carbon, hydrogen and sulfur analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Duplicate sulfur analyses were carried out in this laboratory. All NMR spectra were obtained in CHCl₃ or CH₃CN on a Varian A60 Spectrometer. The spectra of all compounds used in this section were obtained with a Perkin Elmer 221 or 421 Spectrophotometer. Optical rotations were measured with a Rudolph Model 80 Polarimeter in reagent acetone, spectro grade acetonitrile, or pure liquid. When possible a 5% solution was employed. All melting points are uncorrected and were obtained with a Gallenkamp Melting Point Apparatus.

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